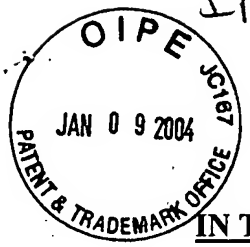
Image 1/12/04 1624



Our Ref.: 427.010-1-1

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	:	B. Kifle
DENNIS BIGG et al	:	
Serial No.: 10/071,046	:	Group: 1624
Filed: February 6, 2000	:	
For: NEW...CONTAINING THEM	:	

475 Park Avenue South
New York, N.Y. 10016
January 9, 2004

SUPPLEMENTAL RESPONSE

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Supplemental to the response filed October 31, 2003, Applicants are submitting herewith a certified copy of French priority application No. 99/02398 filed February 26, 1999 as well as a sworn English translation thereof. This means that the present application is therefor entitled to this date which is prior to the March 3, 1999 effective date of Burke et al patent and the same is therefor no longer a proper reference for the present application.

EV404166797US

"Express Mail" mailing label No. JAN 9, 2004
Date of Deposit
I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to the Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450

D. Malcolm

It is believed that in view of the arguments presented in the October 31, 2003 response and the present response, the claims now clearly point out Applicants' patentable contribution and favorable reconsideration of the application is requested.

Respectfully submitted,
Muserlian, Lucas and Mercanti

Charles A. Muserlian, 19,683
Attorney for Applicants
Tel. # (212) 661-8000

CAM:ds
Enclosures

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF TRANSLATION

Honourable Commissioner of
Patents and Trademarks
Washington, D.C. 20231

Sir:

I, JOHN CHARLES McGILLEY, B.A. M.I.T.I., Technical Translator, of c/o Priory Translations Limited, 11, Magdalen Street, Colchester, Essex, England,

hereby state:

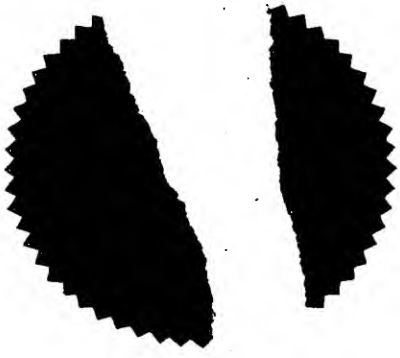
THAT I am well acquainted with the French and English languages.

THAT I translated the document identified as the Certificate of the French National Institute of Industrial Property and of the certified true copy of the French Patent Application No. 99 02398 filed at the National Institute of Industrial Property on 26th February 1999, from French into English;

THAT the attached English translation is a true and correct translation of French Patent Application No. 99 02398

to the best of my knowledge and belief; and

THAT all statements made of my own knowledge are true and that all statements made on information and belief are believed to be true and further, that these statements are made with the knowledge that wilful false statements and the like are punishable by fine or imprisonment, or both, under Section 1001 Title 18 of the United States Code



JOHN CHARLES McGILLEY

A

FRENCH REPUBLIC

NATIONAL INSTITUTE OF INDUSTRIAL PROPERTY

PATENT OF INVENTION

UTILITY CERTIFICATE - CERTIFICATE OF ADDITION

OFFICIAL COPY

The Director General of the National Institute of Industrial Property certifies that the document annexed hereto is the certified true copy of an application for title of industrial property registered at the Institute.

Drawn up in Paris 10 DECEMBER 2003

For the Director of the National
Institute of Industrial Property

The Head of the Patent Department

[signed]
Martine PLANCHE

INVENTION PATENT, UTILITY CERTIFICATE

NATIONAL INSTITUTE OF
INDUSTRIAL PROPERTY

REQUEST FOR GRANT

Confirmation of filing by fax ☐

Date of delivery of documents 26 FEB 1999 National Registration number 99 02398 Postal code of place of filing 75 INPI PARIS Date of filing 26 FEB 1999	**1 NAME AND ADDRESS OF APPLICANT OR REPRESENTATIVE TO WHOM ALL CORRESPONDENCE SHOULD BE ADDRESSED** S.C.A.F. Service brevets et marques 42 rue du Docteur Blanche 75016 PARIS No. of permanent Power of Attorney: LC 041 Ref of correspondent: RS CAS 271 Telephone: 01 44 30 43 56

2. APPLICATION nature of industrial property right

☒ invention patent ☐ divisional application

☐ utility certificate ☐ conversion of a European Patent Application ⇒ **initial application** ⇓ ☐ invention patent ☐ utility certificate No. date

Establishment of search report ☐ deferred ☒ immediate

The Applicant requires payment by instalments of the fees ☐ yes ☐ no

Title of the invention (200 characters maximum)
New optically pure analogues of camptothecin and their preparation process

3. APPLICANT (s) SIREN No. 3 0 8 1 9 7 1 8 5 APE-NAF code 7 4 1 J Name and forenames (underline patronymic name) or name SOCIETE DE CONSEILS DE RECHERCHES ET D'APPLICATIONS SCIENTIFIQUES (S.C.R.A.S.)	Legal form Société anonyme
Nationality French Complete Address 51/53 rue du Docteur Blanche 75016 PARIS	Country FRANCE

4. INVENTOR(S) The inventors are the applicants ☐ yes ☒ no If no, provide a separate designation

5. REDUCTION IN LEVEL OF FEES

6. DECLARATION OF PRIORITY OR REQUEST FOR BENEFIT FROM THE FILING DATE OF A PREVIOUS APPLICATION

7. DIVISIONS previous to the present application

8. SIGNATURE OF APPLICANT OR REPRESENTATIVE [signed] A. BOURGOUIN, Representative	SIGNATURE OF RECEPTION OFFICER	SIGNATURE AFTER REG. OF APPLICATION AT N.I.I.P [signed]

INPI NATIONAL INSTITUTE OF INDUSTRIAL PROPERTY

Patents Administrative Division

DESIGNATION OF INVENTOR
(if the Applicant is not the inventor or the sole inventor)

NATIONAL REGISTRATION NUMBER
9902398

Title of the invention:

New optically pure analogues of camptothecin and their preparation process

The undersigned

SOCIETE DE CONSEILS DE RECHERCHES ET D'APPLICATIONS SCIENTIFIQUES (S.C.R.A.S.)
51/53 rue du Docteur Blanche – 75016 PARIS (FRANCE)

designate(s) as inventor(s) (specify name, forenames, address and underline patronym)

1) LAVERGNE Olivier
6 rue des Anglais
91300 MASSY
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91190 GIF-SUR-YVETTE
FRANCE

3) LANCO Christophe
44 rue Lebrun
91410 DOURDAN
FRANCE

4) ROLLAND Alain
10 rue des Piverts
91120 PALAISEAU
FRANCE

N.B. Exceptionally, the inventor's name can be followed by the name of the company to which he belongs (employing company) if this company is different from the company applying or having title.

Date and signature(s) of applicant(s) or representative

(signed)

A. BOURGOUIN, Representative

25 February 1999

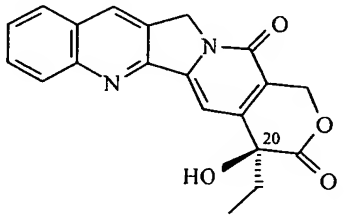
DOCUMENT INCLUDING AMENDMENTS

PAGE(S) OF THE DESCRIPTION OR OF THE CLAIMS OR SHEET(S) OF DRAWINGS			A.C.*	DATE OF THE CORRESPONDENCE	DATE STAMP OF CORRECTOR
Amended	Deleted	Added			
2, 22				30 July 99	AMH – 9 AUG 1999

A change introduced in the drawing up of the original claims, except if the former results from the provisions of article 28 of the decree of 19th September 1979, is indicated by the mention "A.C." (Amended Claims).

New optically pure analogues of camptothecin and their preparation process

Camptothecin is a natural compound which has been isolated for the first time from the leaves and the bark of the Chinese plant called *camptotheca acuminata* (see Wall et al. J. Amer. Chem. Soc. 88:3888 (1966)). Camptothecin is a pentacyclic compound constituted by an indolizino[1,2-b]quinoline fragment fused with an α-hydroxylactone with six links. The carbon in position 20 which carries the α-hydroxy group is asymmetrical and confers a rotatory power on the molecule. The natural form of camptothecin has an absolute "S" configuration as regards the carbon 20 and corresponds to the following formula::



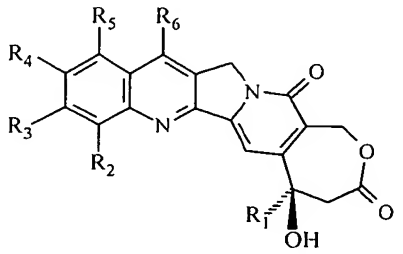
Camptothecin has an anti-proliferative activity in several cancerous cell lines, including the cell lines of human tumors of the colon, lung and breast (Suffness, M et al: The Alkaloids Chemistry and Pharmacology, Bross A., ed., Vol. 25, p. 73 (Academic Press, 1985)). It is suggested that the anti-proliferative activity of camptothecin is related to its inhibitory activity on DNA topoisomerase I.

It has been indicated that α-hydroxylactone was an absolute requirement both for the *in vivo* and *in vitro* activity of camptothecin (Camptothecins: New Anticancer Agents, Putmesil, M et al, ed., p. 27 (CRC Press, 1995); Wall M. et al, Cancer Res. 55:753 (1995); Hertzberg et al, J. Med. Chem. 32:715 (1982) and Crow et al, J. Med. Chem. 35:4160 (1992)). More recently, the Applicant has perfected a new class of analogues of camptothecin, in which β-hydroxylactone replaces the natural α-hydroxylactone of camptothecin (cf. Patent Applications WO 97/00876, WO 98/28304 and WO 98/28305).

A subject of the present Application is a new family of β-hydroxylactonic analogues of camptothecin of the general formula **(I)** described below. A subject is also new β-

hydroxylactonic analogues of camptothecin, the biological activity of which, expressed for example in terms of inhibitory concentrations on the proliferation of tumoral cell colonies, is, unexpectedly, superior to the activity of compounds which are already known. Finally, a subject of the invention is the compounds previously mentioned as medicaments, their use for the production of medicaments as well as pharmaceutical compositions containing them.

The invention firstly relates to the compounds of general formula **(I)**



(I)

in which

R_1	represents a lower alkyl radical;
R_2, R_3, R_4 and R_5	represent, independently, H or a halogen atom;
R_6	represents H, a linear or branched alkyl radical containing 1 to 12 carbon atoms, a cycloalkyl, lower cycloalkyl alkyl, lower hydroxy alkyl or $(CH_2)_mSiR_7R_8R_9$ radical, or also an aryl, or lower aryl alkyl radical, substituted or non substituted on the aryl group in which the substituent is a lower alkyl, a hydroxy group or a halogen atom;
R_7, R_8 and R_9	represent, independently, H or a linear or branched alkyl radical containing 1 to 6 carbon atoms;
m	is an integer comprised between 0 and 6;

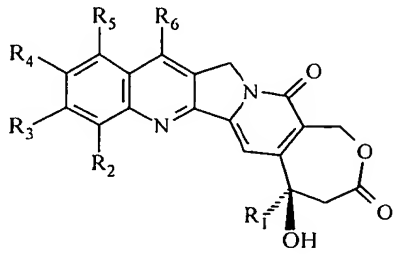
it being understood that when R_3 and R_4 represent two fluorine atoms or two hydrogen atoms, R_6 does not represent H;

or the salts of the latter.

By lower alkyl radical is meant in the present Application a linear or branched alkyl radical containing 1 to 6 carbon atoms. The term cycloalkyl designates a ring with 3 to 7 carbons, such as for example the cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl groups. The term aryl designates a mono-, di- or tricyclic hydrocarbon compound with

at least one aromatic ring, each ring containing a maximum of 7 members, such as for example phenyl, naphthyl, anthracyl, biphenyl or indenyl. The term halo signifies chloro, bromo, iodo or fluoro. The terms lower cycloalkyl alkyl, lower hydroxy alkyl and lower aryl alkyl refer to radicals in which the alkyl chain can be linear or branched and contains 1 to 6 carbon atoms.

The invention relates in particular to the compounds of general formula **(II)**



(II)

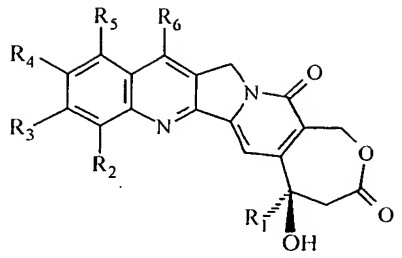
in which

R_1	represents a lower alkyl radical;
R_2, R_3, R_4 and R_5	represent, independently, H or a halogen atom;
R_6	represents H, a linear or branched alkyl radical containing 1 to 12 carbon atoms, a cycloalkyl, lower cycloalkyl alkyl, lower hydroxy alkyl, nitro or $(CH_2)_mSiR_7R_8R_9$ radical, or also an aryl, or lower aryl alkyl radical, substituted or non substituted on the aryl group in which the substituent is a lower alkyl, a hydroxy group or a halogen atom;
R_7, R_8 and R_9	represent, independently, H or a linear or branched alkyl radical containing 1 to 6 carbon atoms;
m	is an integer comprised between 0 and 6;

it being understood that when R_2 represents H, R_6 represents a $(CH_2)_mSiR_7R_8R_9$ radical or a linear or branched alkyl radical containing 7 to 12 carbon atoms;

or the salts of the latter.

The invention relates more particularly to the compounds of general formula **(III)**



(III)

in which

R_1	represents a lower alkyl radical;
R_2, R_3, R_4 and R_5	represent, independently, H or a halogen atom;
R_6	represents $(CH_2)_mSiR_7R_8R_9$;
R_7, R_8 and R_9	represent, independently, H or a linear or branched alkyl radical containing 1 to 6 carbon atoms;
m	is an integer comprised between 0 and 6;

or the salts of the latter.

Particularly preferred compounds for the invention are those for which R_1 represents an ethyl radical, as well as those for which R_3 represents a halogen atom and in particular a fluorine atom.

The invention relates in particular to the following compounds described in the examples:

- (5*R*)-5-ethyl-11-fluoro-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-5-ethyl-9-fluoro-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-5-ethyl-8-fluoro-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6;7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-12-benzyl-5-ethyl-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-12-butyl-5-ethyl-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-5,12-diethyl-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-5-ethyl-5-hydroxy-12-phenyl-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-12-cyclohexyl-5-ethyl-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-5-ethyl-5-hydroxy-12-(4-methylphenyl)-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-10-chloro-5-ethyl-12-(2-fluorophenyl)-5-hydroxy-12-(4-methylphenyl)-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-5-ethyl-9,10-difluoro-5-hydroxy-12-phenyl-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-5-ethyl-9-fluoro-5-hydroxy-12-phenyl-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-12-butyl-5-ethyl-9,10-difluoro-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-12-benzyl-5-ethyl-9,10-difluoro-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-5-ethyl-9,10-difluoro-5-hydroxy-12-propyl-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-5,12-diethyl-9,10-difluoro-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-5-ethyl-9,10-difluoro-5-hydroxy-12-(2-trimethylsilylethyl)-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-5-ethyl-9,11-difluoro-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-12-butyl-5-ethyl-9,11-difluoro-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-5,12-diethyl-9,11-difluoro-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-5-ethyl-5-hydroxy-12-propyl-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-5-ethyl-5-hydroxy-12-(2-trimethylsilylethyl)-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-12-butyl-5-ethyl-9-fluoro-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-5,12-diethyl-9-fluoro-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

-(5*R*)-5-ethyl-5-hydroxy-12-isopentyl-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino [3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-5-ethyl-12-(4-fluorophenyl)-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino [3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-12-(2,6-difluorophenyl)-5-ethyl-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino [3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-12-(3,5-difluorophenyl)-5-ethyl-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-5-ethyl-5-hydroxy-12-(3,4,5-trifluorophenyl)-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-5-ethyl-5-hydroxy-12-(2,4,6-trifluorophenyl)-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-5-ethyl-5-hydroxy-12-(2,3,5,6-tetrafluorophenyl)-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-5-ethyl-5-hydroxy-12-(2,3,4,5,6-pentafluorophenyl)-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-5-ethyl-9-fluoro-12-(4-fluorophenyl)-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-12-(2,6-difluorophenyl)-5-ethyl-9-fluoro-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-12-(3,5-difluorophenyl)-5-ethyl-9-fluoro-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-5-ethyl-9-fluoro-5-hydroxy-12-(3,4,5-trifluorophenyl)-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-5-ethyl-9-fluoro-5-hydroxy-12-(2,4,6-trifluorophenyl)-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-5-ethyl-9-fluoro-5-hydroxy-12-(2,3,5,6-tetrafluorophenyl)-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-5-ethyl-9-fluoro-5-hydroxy-12-(2,3,4,5,6-pentafluorophenyl)-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-5-ethyl-9,10-difluoro-12-(4-fluorophenyl)-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-12-(2,6-difluorophenyl)-5-ethyl-9,10-difluoro-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-12-(3,5-difluorophenyl)-5-ethyl-9,10-difluoro-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-5-ethyl-9,10-difluoro-5-hydroxy-12-(3,4,5-trifluorophenyl)-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-5-ethyl-9,10-difluoro-5-hydroxy-12-(2,4,6-trifluorophenyl)-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-5-ethyl-9,10-difluoro-5-hydroxy-12-(2,3,5,6-tetrafluorophenyl)-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-5-ethyl-9,10-difluoro-5-hydroxy-12-(2,3,4,5,6-pentafluorophenyl)-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-5-ethyl-9,11-difluoro-12-(4-fluorophenyl)-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-12-(2,6-difluorophenyl)-5-ethyl-9,11-difluoro-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-12-(3,5-difluorophenyl)-5-ethyl-9,11-difluoro-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-5-ethyl-9,11-difluoro-5-hydroxy-12-(3,4,5-trifluorophenyl)-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-5-ethyl-9,11-difluoro-5-hydroxy-12-(2,4,6-trifluorophenyl)-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-5-ethyl-9,11-difluoro-5-hydroxy-12-(2,3,5,6-tetrafluorophenyl)-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-5-ethyl-9,11-difluoro-5-hydroxy-12-(2,3,4,5,6-pentafluorophenyl)-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-5-ethyl-9-fluoro-5-hydroxy-12-propyl-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-5-ethyl-9-fluoro-5-hydroxy-12-(3,3,3-trifluoropropyl)-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-5-ethyl-9-fluoro-5-hydroxy-12-isopentyl-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-5-ethyl-9-fluoro-5-hydroxy-12-pentyl-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-5-ethyl-9-fluoro-5-hydroxy-12-phenethyl-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-12-decyl-5-ethyl-9-fluoro-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-12-(2-cyclohexylethyl)-5-ethyl-9-fluoro-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-12-(3,3-dimethylbutyl)-5-ethyl-9-fluoro-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-5-ethyl-9,10-difluoro-5-hydroxy-12-propyl-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-5-ethyl-9,10-difluoro-5-hydroxy-12-(3,3,3-trifluoropropyl)-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-5-ethyl-9,10-difluoro-5-hydroxy-12-isopentyl-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-5-ethyl-9,10-difluoro-5-hydroxy-12-pentyl-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-5-ethyl-9,10-difluoro-5-hydroxy-12-phenethyl-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-12-decyl-5-ethyl-9,10-difluoro-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-12-(2-cyclohexylethyl)-5-ethyl-9,10-difluoro-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-12-(3,3-dimethylbutyl)-5-ethyl-9,10-difluoro-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-5-ethyl-9,11-difluoro-5-hydroxy-12-propyl-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-5-ethyl-9,11-difluoro-5-hydroxy-12-(3,3,3-trifluoropropyl)-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-5-ethyl-9,11-difluoro-5-hydroxy-12-isopentyl-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-5-ethyl-9,11-difluoro-5-hydroxy-12-pentyl-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-5-ethyl-9,11-difluoro-5-hydroxy-12-phenethyl-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-12-decyl-5-ethyl-9,11-difluoro-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-12-(2-cyclohexylethyl)-5-ethyl-9,11-difluoro-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-12-(3,3-dimethylbutyl)-5-ethyl-9,11-difluoro-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

or the salts of the latter.

The invention more particularly relates to the following compounds:

- (5*R*)-12-butyl-5-ethyl-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-5,12-diethyl-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-5-ethyl-5-hydroxy-12-phenyl-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-5-ethyl-9,10-difluoro-5-hydroxy-12-phenyl-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-12-butyl-5-ethyl-9,10-difluoro-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-5-ethyl-9,10-difluoro-5-hydroxy-12-propyl-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-5,12-diethyl-9,10-difluoro-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-5-ethyl-9,10-difluoro-5-hydroxy-12-(2-trimethylsilylethyl)-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-5,12-diethyl-9,11-difluoro-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-5-ethyl-5-hydroxy-12-(2-trimethylsilylethyl)-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-12-butyl-5-ethyl-9-fluoro-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-5,12-diethyl-9-fluoro-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

or the salts of the latter.

The invention most particularly relates to the following compounds:

- (5*R*)-12-butyl-5-ethyl-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-5-ethyl-9,10-difluoro-5-hydroxy-12-phenyl-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-12-butyl-5-ethyl-9,10-difluoro-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-5-ethyl-9,10-difluoro-5-hydroxy-12-propyl-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-5,12-diethyl-9,10-difluoro-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-5-ethyl-9,10-difluoro-5-hydroxy-12-(2-trimethylsilylethyl)-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

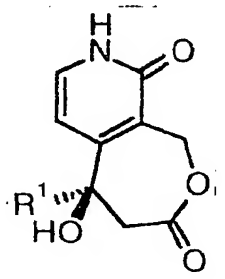
- (5*R*)-5,12-diethyl-9,11-difluoro-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-12-butyl-5-ethyl-9-fluoro-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-5,12-diethyl-9-fluoro-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

or the salts of the latter.

Then again, the invention relates to a key intermediate for the synthesis of compounds of general formula **(I)**, namely a product of general formula

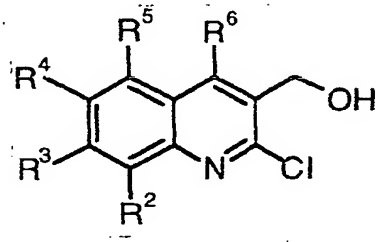


M

in which R_1 has the meaning indicated above. Preferably, R_1 represents an ethyl radical.

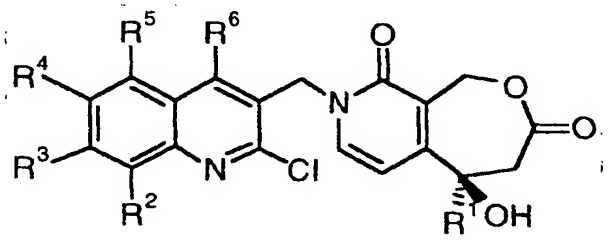
The compounds of general formula **(I)** can be prepared in the following manner:

- the compound of formula **M** is coupled with a compound of formula



N

in which R_2, R_3, R_4, R_5 and R_6 have the meaning indicated above, to produce the compound of formula



O

in which R_2, R_3, R_4, R_5 and R_6 have the meaning indicated above.

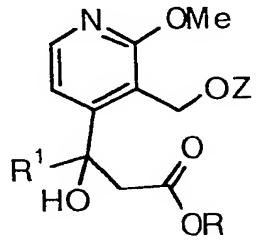
- compound **O** is then cyclized to produce the compound of formula **(I)**.

The formation of compounds **O** starting from the compounds of general formulae **M** and **N** is carried out by a treatment known to a person skilled in the art under the name of Mitsunobu's reaction (refer to Mitsunobu, O. et al. *Synthesis*, p.1 (1981)). The hydroxyl function of compound **N** is displaced by a nucleophile such as compound **M** or a deprotonated derivative of the latter, by a treatment with a phosphine, for example triphenylphosphine, and an azodicarboxylate derivative, for example diethyl or diisopropyl azodicarboxylate, in an aprotic solvent such as, for example, tetrahydrofuran or *N,N*-dimethylformamide. The cyclization of compounds **O** to produce the compounds of formula (I) is preferably carried out in the presence of a palladium catalyst (for example palladium diacetate) under basic conditions (provided for example by an alkaline acetate optionally combined with a phase transfer agent, such as, for example, tetrabutylammonium bromide), in an aprotic solvent such as acetonitrile or *N,N*-dimethylformamide, at a temperature comprised between 50°C and 120°C (R. Grigg et al., *Tetrahedron* **46**, page 4003 (1990)).

The invention also offers, as a new industrial product, a compound of general formula **M** as defined previously. This product can be used for the manufacture of medicaments.

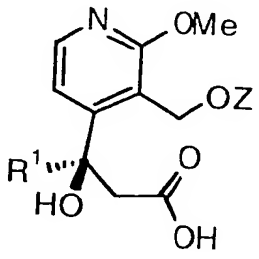
The compound of formula **M** is prepared according to a new process which is part of the invention and includes the following successive stages:

- a racemic ester represented below



in which R_1 has the meaning indicated above, R is a lower alkyl and Z a protective group of the alcohol function (for its preparation, see in particular the Patent Application WO 97/00876) is converted to the corresponding carboxylic acid;

- this compound is then subjected to an operation which separates the enantiomers, known to the person skilled in the art under the name of resolution (cf Jacques, et al., "*Enantiomers, Racemates and Resolution*", 2nd edition, Wiley, New-York, **1991**), and which allows an enantiomerically enriched compound of general formula

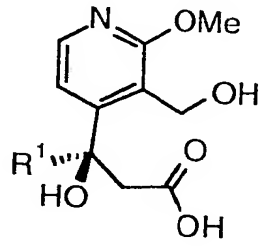


A

to be obtained

in which R_1 and Z have the meaning indicated above;

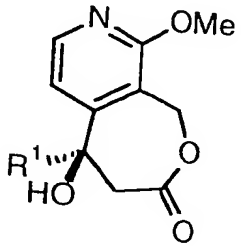
- the alcohol function of the compound of general formula **A** is then deprotected to produce the product of general formula



B

in which R_1 has the meaning indicated above,

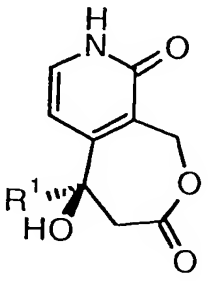
- the compound of general formula **B** is then cyclized in order to obtain the compound of general formula



C

in which R_1 has the meaning indicated above,

- finally, the methoxy group of the compound of general formula **C** is converted to carbonyl in order to obtain a compound of general formula

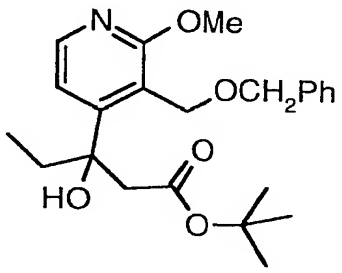


M

in which R_1 has the meaning indicated above.

In the particular case where R_1 represents an ethyl group, R represents a *tert*-butyl and Z represents a benzyl group, the compound of formula **M** is synthesized according to the process constituted by the following successive stages:

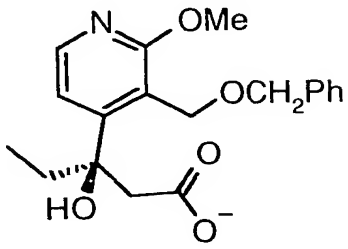
- the racemic *t*-butyl ester represented below (for its preparation, refer in particular to the Patent Application WO 97/00876)



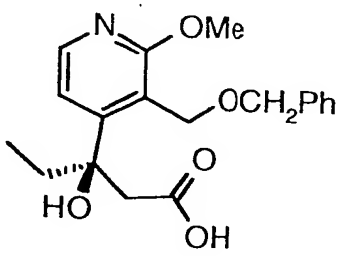
is treated with trifluoroacetic acid for 18 hours at ambient temperature to produce the corresponding carboxylic acid;

- the quinidine salt of 3-(3-benzyloxymethyl-2-methoxy-4-pyridyl)-3-hydroxy-pentanoic acid is heated at a temperature greater than 30°C, and preferably approximately 50°C in isopropyl alcohol, before the reaction medium is allowed to cool down to ambient temperature so that the (+) enantiomer salt of 3-(3-benzyloxymethyl-2-methoxy-4-

pyridyl)-3-hydroxy-pentanoic acid crystallizes whilst the (-) isomer salt, the anion of which is represented below, remains in solution

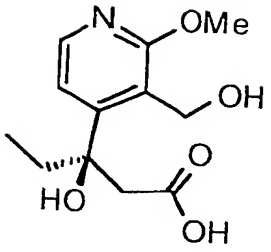


- the solution in isopropyl alcohol of the (-) enantiomer salt of 3-(3-benzyloxymethyl-2-methoxy-4-pyridyl)-3-hydroxy-pentanoic acid is concentrated and treated with hydrochloric acid to produce the compound of formula



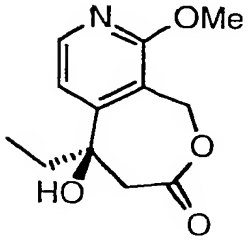
A'

- compound **A'** is then put in contact with palladium in the presence of a hydrogen source to produce the debenzylated product of formula



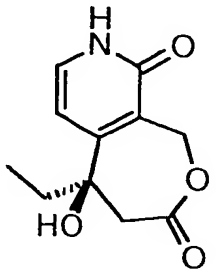
B '

- the compound of formula **B'** is then cyclized in order to obtain the compound of formula



C '

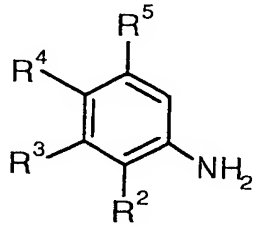
- finally, the methoxy group of the compound of formula **C'** is converted to carbonyl in order to obtain (+)-5-ethyl-5-hydroxy-1,3,4,5,8,9-hexahydrooxepino[3,4-c]pyridin-3,9-dione (or (+)-EHHOPD) represented below.



(+)-EHHOPD

For the process described above, the reaction leading from the compound of formula **A'** to the compound of formula **B'** preferably takes place in methanol, and preferably by heating the reaction medium to about 40°C after the addition of ammonium formate. The cyclization of the compound of formula **B'** to produce compound **C'** can be carried out in THF, preferably at a temperature of about 50°C, while the reaction will preferably be carried out at ambient temperature with acetonitrile as solvent in the reaction leading from the compound of formula **C'** to (+)-EHHOPD.

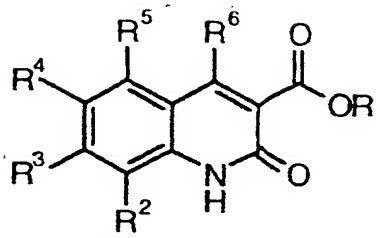
The compounds of formula **N**, in which and R_6 is a hydrogen atom and R_2, R_3, R_4 and R_5 have the meaning indicated above, can be obtained from anilines of formula



P

in which R_2, R_3, R_4 and R_5 have the meaning indicated above, according to the following process: an aniline of formula **P** is *N*-acetylated by treatment with an acetylating agent such as, for example, acetic anhydride. The acetanilide thus obtained is treated at a temperature comprised between 50°C and 100°C, preferably about 75°C, with a reagent known to a person skilled in the art under the name Vilsmeier's reagent (obtained by the action of phosphoryl oxychloride on *N,N*-dimethylformamide at a temperature comprised between 0°C and 10°C) to produce the corresponding 2-chloro-3-quinolinecarbaldehyde (for example, refer to Meth-Cohn et al. *J. Chem. Soc., Perkin Trans. I* p.1520 (1981); Meth-Cohn et al. *J. Chem. Soc., Perkin Trans. I* p.2509 (1981); and Nakasimhan et al. *J. Am. Chem. Soc., 112* p.4431 (1990)). This intermediate is easily reduced to the corresponding quinolylmethanol of formula **N**, under standard conditions known to a person skilled in the art such as treatment in an alcoholic solvent (for example methanol) with sodium borohydride at a temperature comprised between 0°C and 40°C.

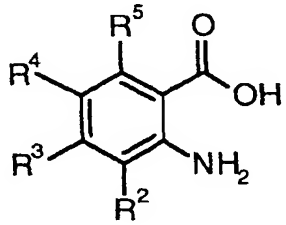
The compounds of formula **N** in which R_2, R_3, R_4, R_5 and R_6 have the meaning indicated above, can also be obtained from carboxylated quinolones of formula



Q

in which R_2, R_3, R_4, R_5 and R_6 have the meaning indicated above, according to the following process: a quinolone of formula **Q** is chlorinated to produce the corresponding chloroquinoline, the carboxylated function of which is reduced to produce the compound of general formula **N**. The chlorination can be carried out with a chlorophosphine oxide such as phosphorus oxychloride or chlorodiphenylphosphine oxide, pure or in the presence of an inert aprotic cosolvent such as toluene or chloroform, at a temperature comprised between 50°C and 120°C. The chlorination is preferably carried out with an excess of phosphorus oxychloride at 80°C. The reduction can be carried out with an aluminium hydride in an aprotic solvent such as diethyl ether, *tert*-butylmethyl oxide, tetrahydrofuran, dichloromethane, chloroform, trichloroethane or toluene, at a temperature comprised between 0°C and 50°C. The reduction is preferably carried out with diisobutylaluminium hydride in dichloromethane at ambient temperature.

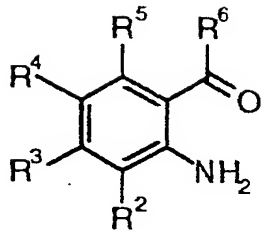
The compounds of formula **Q**, in which and R_6 is a hydrogen atom and R_2, R_3, R_4 and R_5 have the meaning indicated above, can be obtained from anthranilic acids of formula



in which R_6 is a hydrogen atom and R_2, R_3, R_4 and R_5 have the meaning indicated above, according to the following process: an acid of formula **R** is reduced to produce

the corresponding benzyl alcohol. The alcohol function of the intermediate thus obtained is protected selectively in order to leave the amine function intact. The resulting aniline is acylated with a derivative of malonic acid. The previously protected alcohol function is deprotected, then oxidized to produce the corresponding carbonyl function, and the intermediate thus obtained is subjected to an intermolecular process according to a reaction known to a person skilled in the art under the name of Knoevenagel's condensation, to produce carboxylated quinolones of formula **Q**, in which and R_6 is a hydrogen atom and R_2, R_3, R_4 and R_5 have the meaning indicated above. The reduction of the acid to alcohol can be carried out by a metallic hydride in an inert aprotic solvent at a temperature comprised between 0°C and 50°C, and preferably by a mixed hydride of lithium and aluminium in tetrahydrofuran at ambient temperature. The protection of the intermediate benzyl alcohol can be carried out according to the general methods known to the person skilled in the art (Greene T, et al., "*Protective groups in Organic Synthesis*", 2nd edition, Wiley, New-York, **1991**) or also with a silyl chloride in the presence of a base, in an aprotic solvent at a temperature comprised between 0°C and 50°C, and preferably by *tert*-butyldiphenylsilyl chloride in the presence of imidazole, in dimethylformamide at ambient temperature. Acylation can be carried out with a malonic derivative such as ethylmalonyl chloride or methyl malonate in the presence of a base such as triethylamine or 4-dimethylaminopyridine in an aprotic solvent such as acetonitrile, tetrahydrofuran or toluene at a temperature comprised between 0°C and 110°C, and preferably with ethylmalonyl chloride in acetonitrile at ambient temperature in the presence of triethylamine. Deprotection can be carried out according to the protective group of the benzyl alcohol previously chosen (Greene, T.) and in the case of silylated ether by a fluoride ion source such as cesium or potassium fluoride in the presence of a phase transfer agent, or also tetrabutylammonium fluoride in an aprotic solvent such as tetrahydrofuran at a temperature comprised between 0°C and 50°C and preferably at ambient temperature. The oxidation can be carried out in the presence of chromium (VI) salts carrying pyridyl ligands, by Swern's reagent, or also by pyridine-sulphur trioxide complex in dimethyl sulphoxide in the presence of triethylamine, and preferably by pyridinium dichromate in dichloromethane at ambient temperature. Knoevenagel's intermolecular condensation can be carried out spontaneously or in solution in the presence of a base, and preferably in dichloromethane in the presence of triethylamine at ambient temperature.

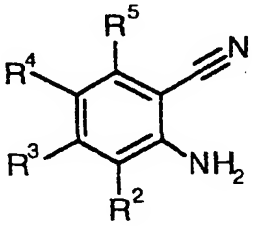
The compounds of formula **Q**, in which R_2, R_3, R_4, R_5 and R_6 have the meaning indicated above, can be obtained from aminoketones of formula



S

in which R_2, R_3, R_4, R_5 and R_6 have the meaning indicated above, according to the following process: an aminoketone **S** is acylated with a derivative of malonic acid and the intermediate thus obtained is subjected to an intermolecular process according to a reaction known to a person skilled in the art under the name of Knovenagel's condensation to produce carboxylated quinolones of formula **Q**. Acylation can be carried out with a malonic derivative such as ethylmalonyl chloride or methyl malonate in the presence of a base such as triethylamine or 4-dimethylamino-pyridine in an aprotic solvent such as acetonitrile, tetrahydrofuran or toluene at a temperature comprised between 0°C and 110°C, and preferably with ethylmalonyl chloride in acetonitrile at ambient temperature in the presence of triethylamine. Knovenagel's intermolecular condensation can be carried out spontaneously or in solution in the presence of a base, and preferably in acetonitrile in the presence of sodium ethylate at ambient temperature.

The aminoketones of formula **S**, in which R_2, R_3, R_4, R_5 and R_6 have the meaning indicated above, can be obtained from ortho-aminated benzonitriles of formula



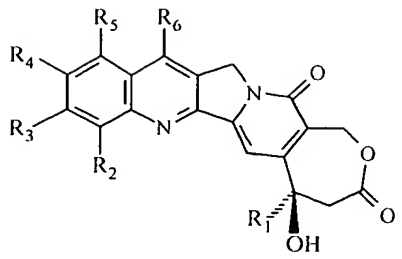
in which R_2, R_3, R_4 and R_5 have the meaning indicated above, by treatment with a Grignard's reagent of formula R_6-MgX, where X is a halogen and R_6 has the meaning above according to methods known to the person skilled in the art.

The aminoketones of formula **S**, in which R_6 is an aryl radical and R_2, R_3, R_4 and R_5 have the meaning indicated above, can be obtained from anthranilic acids of formula **R** described above, by treatment with benzoyl chloride under reflux to produce a benzoxazone which can be converted in the presence of Grignard's reagent of formula R_6-MgX, where X is a halogen and R_6 is an aryl radical to the corresponding ortho-aminated benzophenone, which can be debenzoylated by reagents such as, for example, hydrogen bromide in solution in water or in glacial acetic acid.

The aminoketones of formula **S**, in which R_2, R_3, R_4, R_5 and R_6 have the meaning indicated above, can be obtained from anilines of formula **P** in which R_2, R_3, R_4 and R_5 have the meaning indicated above, according to the following process: The nitrogen atom of an aniline of formula **P** is acylated with an agent conferring an ortho-directive character in the aryl metallation reaction, and the compound thus obtained is metalated, then treated with an aldehyde of formula R_6-CHO in which R_6 has the meaning above. The process is then completed by oxidation of the alcoholic intermediate thus obtained, then by release of the nitrogenous function to produce an aminoketone of formula **S**. For this process, passage to the ortho-directive function can be obtained by treating an aniline **P** with a "bocant" agent and preferably by di-*tert*-butyl dicarbonate in an aprotic solvent such as tetrahydrofuran, dioxane or dimethoxyethane at reflux temperature. The metallation can be obtained by treatment with a lithiated reagent such as *tert*-butyllithium, *sec*-butyllithium, mesityllithium, or, in the presence of tetramethyl-ethylenediamine, *n*-butyllithium, and preferably *n*-butyllithium in the presence of tetramethyl-ethylenediamine, in an aprotic solvent such as tetrahydrofuran, dioxane or dimethoxyethane, at a temperature comprised between -80°C and 0°C. Oxidation can be carried out in the presence of chromium (VI) salts carrying pyridyl ligands, by Swern's reagent, or also by the pyridine-sulphur trioxide complex in dimethylsulphoxide in the presence of triethylamine, and preferably by pyridinium dichromate in dichloromethane under reflux. The nitrogenous function can be obtained by treatment in acid medium, and preferably by trifluoroacetic acid in dichloromethane at ambient temperature.

Analogues of intermediate compounds of type **N** have been described previously and in particular in the PCT Application WO 95/05427.

The compounds of formula **(I)**

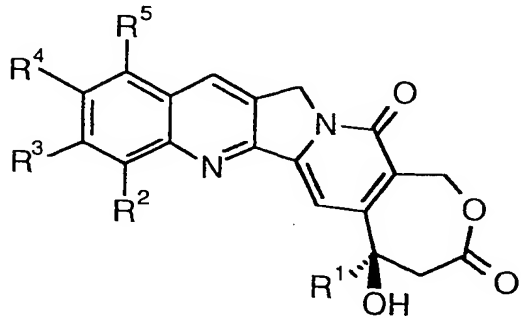


(I)

in which

R_1	represents a lower alkyl radical;
R_2, R_3, R_4 and R_5	represent, independently, H or a halogen atom;
R_6	represents H, a linear or branched alkyl radical containing 1 to 12 carbon atoms, a cycloalkyl, lower cycloalkyl alkyl, lower hydroxy alkyl, nitro or $(CH_2)_mSiR_7R_8R_9$ radical, or also an aryl or lower aryl alkyl radical, substituted or non substituted, in which the substituent is a lower alkyl, a hydroxy group or a halogen atom;
R_7, R_8 and R_9	represent, independently, H or a linear or branched alkyl radical containing 1 to 6 carbon atoms;
m	is an integer comprised between 0 and 6;

can also be obtained by a new process, characterized in that a compound of formula



(IV)

in which R_1, R_2, R_3, R_4 and R_5 have the meaning indicated above, is treated in a strongly acid medium in the presence of an iron (III) salt and a precursor of the free radical $R_6^{\bullet}$, by a solution containing hydroxide or alkoxide radicals.

Although the prior art mentions the use of a similar reaction for the analogues of camptothecines containing an α-hydroxylactone (Sawada, S., et al., *Chem Pharm. Bull.*, (1991), vol. **39**, p. 2574); PCT Application WO 98/35940), its use for the analogues of camptothecines such as the compounds of formula **(IV)** containing a β-hydroxylactone, has not been foreseen and is unexpected, because in strongly acid medium, a ternary and benzylic hydroxyl function, in position β with regard to a carboxylic function, is generally eliminated to produce the corresponding olefine (Nagasawa, et al. *Heterocycles* 1989, vol. **28**, p. 703; Kimura, H. et al., *Chem. Pharm. Bull.* 1982, vol. **30**, p. 552; Fujita, T. et al., *J. Appl Chem Biotechnol.* 1982, vol. **32**, p. 421; Miller, R. E., et al., *J. Org. Chem.* 1950, vol. **15**, p. 89; Fieser, L. F., et al., J. Am. Chem. Soc. 1948, vol. **70**, p. 3209).

In the process above, the strongly acid medium can be provided by acids such as aqueous or non-aqueous trifluoroacetic acid or sulphuric acid and preferably aqueous sulphuric acid, the iron (III) salt will preferably be heptahydrated iron (III) sulphate, the free radical precursor will be an aldehyde of formula R_6-CHO in which R_6 represents a lower alkyl, cycloalkyl, lower cycloalkyl alkyl, lower hydroxy alkyl, $(CH_2)_mSiR_7R_8R_9$, or also a substituted or non substituted lower arylalkyl in which the substituent is a lower alkyl, a hydroxy group or a halogen atom, and the solution containing hydroxide or alkoxide radicals is provided by hydrogen peroxide or *tert*-butyl hydroperoxide, and preferably by hydrogen peroxide at 30 volumes.

The compounds of the present invention posses useful pharmacological properties. Therefore it follows that the compounds of the present invention have an inhibitory activity on topoisomerase I and/or II and an anti-tumoral activity. The state of the art suggests that the compounds of the invention have an anti-parasitic and/or anti-viral activity. The compounds of the present invention can thus be used in different therapeutic applications.

An illustration of the pharmacological properties of the compounds of the invention will be found hereafter in the experimental part.

The compounds can inhibit topoisomerase, for example of type I and/or II, in a patient, for example a mammal such as man, by administration to this patient of a therapeutically effective quantity of the compounds of the invention.

The compounds of the invention have an anti-tumoral activity. They can be used for the treatment of tumors, for example of tumors expressing a topoisomerase, in a patient by administration to said patient of a therapeutically effective quantity of one of the

compounds of the invention. Examples of tumors or cancers include cancers of the oesophagus, the stomach, the intestines, the rectum, the oral cavity, the pharynx, the larynx, the lung, the colon, the breast, the cervix uteri, the corpus endometrium, the ovaries, the prostate, the testicles, the bladder, the kidneys, the liver, the pancreas, the bone, the connective tissues, the skin, for example melanomas, the eyes, the brain and the central nervous system, as well as cancer of the thyroid, leukemia, Hodgkin's disease, lymphomas other than those related to Hodgkin, multiple myelomas and others.

They can also be used for the treatment of parasitic infections by inhibition of the hemoflagellates (for example in trypanosomia or leishmania infections) or by inhibition of the plasmodia (such as for example in malaria), but also the treatment of viral infections or diseases.

These properties make the compounds of the invention suitable for pharmaceutical use. A subject of the present Application is also the compounds of the invention, and in particular the products of general formulae **(I)** or **(II)** as defined above as medicaments. The invention also relates to pharmaceutical compositions containing at least one of the medicaments as defined above as an active ingredient.

Therefore the invention relates to pharmaceutical compositions containing a compound according to the invention or an addition salt with a pharmaceutically acceptable acid of it, in combination with a pharmaceutically acceptable support according to the chosen administration method (for example oral, intravenous, intraperitoneal, intramuscular, trans-dermic or sub-cutaneous). The pharmaceutical composition (for example therapeutic) can be in the form of a solid, liquid, liposome or lipidic micella.

The pharmaceutical composition can be in solid form, such as for example, powders, pills, granules, tablets, liposomes, gelatin capsules or suppositories. The pill, tablet or gelatin capsule can be covered in a substance which is capable of protecting the composition from the action of gastric acid or enzymes in the stomach of the subject for a sufficient period of time to allow this composition to pass in a non-digested form into the small intestine of the latter. The compound can also be administered locally, for example, at the same location as the tumor. The compound can also be administered according to a sustained release process (for example a sustained release composition or an infusion pump). The appropriate solid supports can be, for example, calcium phosphate, magnesium stearate, magnesium carbonate, talc, sugars, lactose, dextrin, starch, gelatin, cellulose, methyl cellulose, sodium carboxymethyl cellulose, polyvinylpyrrolidine and wax. The pharmaceutical compositions containing a compound according to the invention can also be presented in liquid form such as, for

example, solutions, emulsions, suspensions or a sustained release formulation. The appropriate liquid supports can be, for example, water, organic solvents such as glycerol or glycols such as polyethylene glycol, similarly their mixtures, in varied proportions, in water.

A subject of the invention is also the use of the compounds of the invention for the preparation of medicaments intended to inhibit topoisomerases, and more particularly the topoisomerases of type I or of type II, medicaments intended to treat tumors, medicaments intended to treat parasitic infections, as well as medicaments intended to treat viral infections or diseases.

The dose of a compound according to the present invention envisaged for the treatment of the diseases or disorders mentioned above, varies according to the administration method, the age and body weight of the subject as well as the state of the latter and it will be decided definitively by the attending doctor or vet. Such a quantity determined by the attending doctor or vet is here called "effective therapeutic quantity".

Unless defined in another manner, all the technical and scientific terms used here have the same meaning as that commonly understood by an ordinary specialist in the field to which the invention belongs. Similarly, all publications, Patent Applications, all Patents and all other references mentioned here are incorporated by way of reference.

The following examples are presented to illustrate the above procedures and must in no case be considered as a limit to the scope of the invention.

EXPERIMENTAL PART:

Example 1: **(5*R*)-5-ethyl-11-fluoro-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione**

Stage 1a. quinidinium (3*R*)- 3-(3-benzyloxymethyl-2-methoxy-4-pyridyl)-3-hydroxy-pentanoate.

Tert-butyl 3-(3-benzyloxymethyl-2-methoxy-4-pyridyl)-3-hydroxy-pentanoate (obtained according to the method described in the Patent Application PCT WO 97/00876; 40 g; 100 mmol) is treated with trifluoroacetic acid (150 ml) and the reaction medium is agitated for 18 hours at 20°C, then concentrated under reduced pressure. The residue, taken up in a saturated aqueous solution of sodium bicarbonate (200 ml), is washed with dichloromethane (2 x 100 ml) and the resulting solution is acidified to pH = 1 with 6 N hydrochloric acid, then extracted with dichloromethane (2 x 200 ml). The combined extracts are dried over magnesium sulphate and concentrated. The solution is dried over magnesium sulphate and concentrated. The racemic acid thus obtained (31.1 g; 90 mmol), taken up in isopropyl alcohol (30 ml), is treated with a quinidine solution (29.2 g; 90 mmol) in isopropyl alcohol (30 ml), and the resulting mixture is agitated at 50°C until complete dissolution. The temperature is allowed to reduce to 40°C, the agitation is stopped and the reaction medium allowed to cool down to ambient temperature. The medium is taken to 0°C without agitation then maintained at this temperature for 16 hours. Then the temperature is allowed to rise to 20°C and agitation is carried out until crystallization. The medium is diluted with isopropyl alcohol then filtered. The precipitate is rinsed with isopropyl alcohol. The dextrorotatory salt precipitates whilst the levorotatory salt remains in solution in isopropyl alcohol. The filtrate is recovered which is concentrated to produce the expected product. Analysis by HPLC (column CHIRAL-AGP 5µ (10 cm x 4 mm) eluted with an isopropyl alcohol/water/ phosphate buffer mixture pH 6.5 30/920/50, at a flow rate of 1.2 ml/min, UV detection at 280 nm) shows retention times of 6.4 min for the levorotatory salt and 2.8 min for the dextrorotatory salt and a diastereoisomeric ratio of 83/17.

Stage 1b: (5*R*)-5-ethyl-5-hydroxy-1,3,4,5,8,9-hexahydrooxepino[3,4-c]pyridin-3,9-dione, or (+)-EHHOPD.

The residue obtained in Stage 1a is agitated for 16 hours at 20°C in a mixture of dichloromethane (270 ml) and 1N hydrochloric acid (270 ml). After decanting, the organic phase is concentrated, and the residue is taken up in methanol (87 ml) to be

used in the following phase. This solution is poured under nitrogen onto Palladium at 10% on damp carbon at 50% (27.7 g; 13 mmol). The reaction medium is agitated for 5 min, then poured into a solution of ammonium formate (11.5 g; 183 mmol) in methanol (135 ml). The reaction medium is agitated for 30 min whilst allowing the temperature to rise, then it is heated at 40°C for 30 min. The medium is then filtered on a bed of Clarcel and concentrated. Toluene (40 ml) is poured in followed by evaporation, and this operation is repeated in order to eliminate the traces of methanol. The residue, taken up in tetrahydrofuran (45 ml), is treated with a solution of dicyclohexylcarbodiimide (7.18 g; 34.5 mmol) in tetrahydrofuran (20 ml). The reaction medium is heated at 50°C for 1 hour, then taken to 20°C, and the dicyclohexylurea is filtered. The filtrate is concentrated to dryness and the residue, taken up in acetonitrile (46 ml), is treated with sodium iodide (6.0 g; 40.5 mmol) and trimethylsilyl chloride (5.13 ml; 40.5 mmol). The reaction medium is maintained under agitation at ambient temperature for 5 hours, then acetonitrile (28 ml) and water (5.6 ml) are added. The precipitate obtained is recovered by filtration, then taken up in water (10 ml), and the mixture obtained is neutralized using a solution of ammonium hydroxide. The precipitate is recovered by filtration then taken up in acetone (40 ml) to which water (150 ml) is added. The crystals formed are recovered by filtration and dried to produce 3 g of (+)-EHHOPD with an enantiomeric proportion of 99.4/0.6.

NMR ^{1}H (DMSO-d6, δ): 0.8 (t, 3H); 1.65 (m, 2H); 3.00-3.35 (q, 2H); 5.3 (q, 2H); 5.7 (s, 1H); 6.35 (d, 1H); 7.3 (d, 1H); 11.7 (s, 1H).

Stage 1c: 2-amino-6-fluorophenylmethanol.

A solution under argon of 2-amino-6-fluorobenzoic acid (5 g; 32 mmol) in anhydrous tetrahydrofuran (100 ml) is treated with lithium aluminium hydride (1M in tetrahydrofuran; 64 ml; 64 mmol) at ambient temperature. The reaction medium is agitated for 3 hours, then hydrolyzed at 0°C with a saturated aqueous solution of ammonium chloride (100 ml). The resulting mixture is extracted with ethyl acetate (2 x 70 ml). The combined extracts are washed with water and with a saturated aqueous solution of sodium chloride, then dried over magnesium sulphate and concentrated to produce 3.8 g of the desired product, a white solid (m.p.: 93°C).

IR (KBr): 784, 1001, 1471, 1591, 1621 cm^{-1}.

NMR ^{1}H (DMSO-d6, δ): 4.44 (dd, 2H); 4.93 (t, 1H); 5.27 (s, 2H); 6.27 (t, 1H); 6.45 (d, 1H) ; 6.96 (q, 1H).

Stage 1d: ethyl 2-(3-fluoro-2-hydroxymethylphenylcarbamoyl) acetate.

A solution of aminobenzyl alcohol (obtained in Stage 1c; 3.8 g; 27 mmol) and imidazole (4.3 g; 64 mmol) in *N,N*-dimethylformamide (52 ml) is treated with *tert*-butyldiphenylsilyl chloride (8.37 ml; 32 mmol). The resulting mixture is agitated for 2 hours at ambient temperature, then water (100 ml) is added, followed by extraction with ethyl acetate (2 x 60 ml). The combined extracts are washed with water and with a saturated aqueous solution of sodium chloride, then dried over magnesium sulphate and concentrated. The silylated intermediate thus obtained (10 g) is taken up in acetonitrile (52 ml), then triethylamine (4.5 ml; 32.4 mmol) is added to the solution, and the resulting mixture is treated dropwise with ethylmalonyl chloride (4.15 ml; 32.4 mmol). The resulting mixture is agitated for 2 hours at ambient temperature, then water (100 ml) is added, followed by extraction with ethyl acetate (2 x 60ml). The combined extracts are washed with water and with a saturated aqueous solution of sodium chloride, then dried over magnesium sulphate and concentrated. The residue (16 g) is taken up in tetrahydrofuran (50 ml) and treated dropwise with tetrabutylammonium fluoride (1M in tetrahydrofuran; 27 ml; 27 mmol). The resulting mixture is agitated for 1 hour at ambient temperature, then water (100 ml) is added followed by extraction with ethyl acetate (2 x 60 ml). The combined extracts are washed with water and with a saturated solution of sodium chloride, then dried over magnesium sulphate and concentrated. Purification of the residue by chromatography at medium pressure (SiO_2, CH_2Cl_2/MeOH, 95/5) yields 4.8 g of a white solid (m.p.: 91 °C).

IR (KBr): 1472, 1542, 1589, 1657, 1719, 3286, 3482 cm^{-1}.

NMR ^1H (DMSO-d6, δ): 1.19 (t, 3H); 3.54 (s, 2H); 4.14 (q, 2H); 4.55 (dd, 2H); 5.21 (t, 1H); 6.97 (t, 1H); 7.31 (dd, 1H); 7.53 (d, 1H).

Stage 1e: ethyl 5-fluoro-2-oxo-1,2-dihydro-3-quinolinecarboxylate.

A solution of malonic derivative (obtained in Stage 1d; 4.8 g; 19 mmol) in dichloromethane (280 ml) is treated with pyridinium dichromate (8.3 g; 22 mmol). The resulting suspension is agitated for 4 hours at ambient temperature, then treated with triethylamine (30 ml; 220 mmol). The reaction medium is agitated at ambient temperature for 16 hours, then concentrated under reduced pressure. Purification of the residue by chromatography at medium pressure (SiO_2, CH_2Cl_2/MeOH, 95/5) yields 2.1 g of a yellow solid (m.p.: 180°C).

IR (KBr): 1441, 1498, 1655, 1747 cm^{-1}.

NMR ^1H (DMSO-d6, δ): 1.31 (t, 3H); 4.28 (q, 2H); 7.06 (t, 1H); 7.16 (d, 1H); 7.61 (dd, 1H); 8.43 (s, 1H); 12.27 (s, 1H).

Stage 1f: ethyl 2-chloro-5-fluoro-3-quinolinecarboxylate.

The quinolone (obtained in Stage 1e; 2.1 g) is heated at 80°C in phosphorus oxychloride (14 ml) until the reaction is complete (TLC control: SiO_2, CH_2Cl_2/MeOH, 95/5). The resulting solution is then concentrated under reduced pressure and the residue is taken up in water. The precipitate thus formed is recovered by filtration, washed with water until the pH is neutral, and dried under reduced pressure in the presence of phosphorus pentoxide to produce 1.8 g of a white solid (m.p.: 97°C).
IR (KBr): 1268, 1631, 1723 cm^{-1}.
NMR ^1H (DMSO-d6, δ): 1.38 (t, 3H); 4.42 (q, 2H); 7.60 (t, 1H); 7.89 (d, 1H); 7.97 (dd, 1H); 8.92 (s, 1H).

Stage 1g: 2-chloro-5-fluoro-3-quinolylmethanol.

A solution of quinolinecarboxylate (obtained in Stage 1f; 1.8 g; 6.7 mmol) in dichloromethane (40 ml) under argon is treated dropwise with diisobutylaluminium hydride (1M in dichloromethane; 20 ml; 20 mmol) at ambient temperature maintained at 10°C by an ice-cooled water bath. The reaction mixture is agitated for 1 hour at ambient temperature, then poured onto a solution of sodium and potassium tartrate at 20% (200 ml). The resulting mixture is agitated vigorously for 1 hour, then filtered on celite. The filtrate is extracted with dichloromethane (2 x 100 ml). The combined extracts are washed with water and with a saturated solution of sodium chloride, then dried over magnesium sulphate and concentrated. Purification of the residue by chromatography at medium pressure (SiO_2, CH_2Cl_2/MeOH, 98/2) yields 450 mg of a white solid (m.p.: 176 °C).
NMR ^1H (DMSO-d6, δ): 4.71 (d, 2H); 5.78 (t, 3H); 7.51 (t, 1H); 7,75-7.83 (m, 2H); 8.50 (s, 1H).

Stage 1h: (5*R*)-5-ethyl-11-fluoro-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione.

A solution of quinolylmethanol (obtained in Stage 1g; 422 mg; 2 mmol), of (+)-EHHOPD (obtained in Stage 1b; 446 mg; 2 mmol) and triphenylphosphine (592 mg; 2.2 mmol) in *N,N*-dimethylformamide (8 ml) is treated dropwise with isopropyl azodicarboxylate (0.43 ml; 2.2 mmol). The reaction mixture is agitated for 16 h at ambient temperature, then water (100 ml) is added, followed by extraction with ethyl acetate (2 x 100 ml). The combined extracts are washed with water and with a saturated solution of sodium chloride, then dried over magnesium sulphate and concentrated under reduced pressure. The residue is purified by chromatography at medium pressure (SiO_2, AcOEt/heptane, 30/70). A mixture under argon of the intermediate obtained

(325 mg; 0.78 mmol), triphenylphosphine (42 mg; 0.156 mmol), potassium acetate (114 mg; 1.17 mmol), tetrabutylammonium bromide (276 mg; 0.86 mmol) and palladium acetate (0.078 mmol) is taken to reflux in anhydrous acetonitrile for 16 hours, then cooled down to ambient temperature and concentrated under reduced pressure. The residue is purified by chromatography at medium pressure (SiO_2, $MeOH/CH_2Cl_2$, 5/95) to produce 80 mg of the expected solid (m.p. > 250 °C).

IR (KBr):1659, 1734, 3386 cm^{-1}.

NMR ^1H (DMSO-d6, δ): 0.86 (t, 3H); 1.85 (q, 2H); 3.07 (d, 1H); 3.46 (d, 1H); 5.28 (s, 2H); 5.39 (d, 1H); 5.52 (d, 1H); 6.02 (s, 1H); 7.43 (s, 1H); 7.55 (t, 1H); 7.85 (q, 1H); 8.01 (d, 1H); 8.82 (s, 1H).

Example 2: **(5*R*)-5-ethyl-9-fluoro-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione**

This compound is obtained by applying Stages 1c to 1h of the operating method of Example 1 above to 2-amino-4-fluorobenzoic acid. A solid (m.p. > 250°C) is obtained.

NMR ^1H (DMSO-d6, δ): 0.86 (t, 3H); 1.84 (q, 2H); 3.04 (d, 1H); 3.47 (d, 1H); 5.24 (s, 2H); 5.39 (d, 1H); 5.52 (d, 1H); 6.06 (s, 1H); 7.39 (s, 1H); 7.65 (t, 1H); 7.88 (d, 1H); 8.22 (dd, 1H); 8.71 (s, 1H).

Example 3: **(5*R*)-5-ethyl-8-fluoro-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione**

This compound is obtained by applying Stages 1c to 1h of the operating method of Example 1 above to 2-amino-3-fluorobenzoic acid (prepared according to Muchowski, et al., *J. Org. Chem.*, vol. **45**, p. 4798). A solid (m.p. > 250°C) is obtained.

IR (KBr): 1659, 1731, 3344 cm^{-1}.

NMR ^1H (DMSO-d6, δ): 0.88 (t, 3H); 1.85 (q, 2H); 3.07 (d, 1H); 3.47 (d, 1H); 5.29 (s, 2H); 5.40 (d, 1H); 5.53 (d, 1H); 6.06 (s, 1H); 7.44 (s, 1H); 7.69 (m, 2H); 7.96 (m, 1H); 8.75 (s, 1H).

Example 4: **(5*R*)-12-benzyl-5-ethyl-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione**

Stage 4a: 1-(2-aminophenyl)-2-phenyl-1-ethanone.

A solution of 2-aminobenzonitrile (4.25 g, 36 mmol) in anhydrous diethyl ether (40 ml) at 0°C is treated under argon with benzylmagnesium chloride (2M in tetrahydrofuran; 50 ml; 100 mmol). The reaction medium is maintained under agitation for 1 hour at ambient temperature, then hydrolyzed at 0°C by adding hydrochloric acid at 10%, agitated for 1 hour, and neutralized with soda. The resulting mixture is extracted with ethyl acetate. The combined extracts are washed with water and with a saturated aqueous solution of sodium chloride, then dried over magnesium sulphate and concentrated to produce 3.5 g of the desired product, in the form of a white solid (m.p.: 100-101 °C).

IR (KBr): 1469, 1612, 1725 cm^{-1}

NMR ^{1}H (DMSO-d6, δ): 4.25 (s, 2H); 6.53 (t, 1H); 6.74 (d, 1H); 7,2-7.35 (m, 8H); 7.90 (d, 1H).

Stage 4b: ethyl 4-benzyl-2-oxo-1,2-dihydro-3-quinolinecarboxylate.

A solution of amino-ketone (obtained in Stage 4a; 13.5 g; 16 mmol) and triethylamine (3.9 ml, 28 mmol) in acetonitrile (66 ml) is treated at 10°C dropwise with ethylmalonyl chloride (3.64 ml; 28 mmol). The reaction medium is agitated for 16 hours at ambient temperature, then treated with sodium ethoxide, obtained by dissolution of sodium (0.4 g; 17 mmol) in ethanol (25 ml). The resulting mixture is agitated for 16 hours at ambient temperature, then water is added (200 ml), followed by extraction with dichloromethane (2 x 100 ml). The combined extracts are washed with water and with a saturated solution of sodium chloride, then dried over magnesium sulphate and concentrated. The residue is taken up in ethyl ether to produce a precipitate which is recovered by filtration, dried under reduced pressure at 50°C, to produce the expected solid (m.p.: 230 °C).

NMR ^{1}H (DMSO-d6, δ): 1.19 (t, 3H); 4.17 (s, 2H); 4.27 (q, 2H); 7.13 (t, 1H); 7.15-7.20 (m, 1H); 7.20-7.40 (m, 5H); 7.49 (t, 1H); 7.69 (d, 1H); 12.15 (s, 1H).

Stage 4c: (5*R*)-12-benzyl-5-ethyl-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione.

Stages 1f to 1h of the operating method of Example 1 above are applied to the quinolone obtained according to Stage 4b. A solid is obtained (m.p. > 250 °C).
IR (KBr): 1578, 1655, 1751 cm^{-1}.
NMR ^1H (DMSO-d6, δ): 0.87 (t, 3H); 1.87 (q, 2H); 3.05 (d, 1H); 3.49 (d, 1H); 4.65 (d, 1H); 4.70 (d, 1H); 5.20 (d, 1H); 5.25 (d, 1H); 5.39 (d, 1H); 5.52 (d, 1H); 6.06 (s, 1H); 7.15 – 7.30 (m, 5H); 7.41 (s, 1H); 7.67 (t, 1H); 7.83 (t, 1H); 8.16 (d, 1H); 8.28 (d, 1H).

Example 5: (5*R*)-12-butyl-5-ethyl-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione.

2-aminobenzonitrile is treated with *n*-butylmagnesium bromide according to a procedure similar to Stage 4a and the resulting amino-ketone is treated according to a procedure similar to Stage 4b. Stages 1f to 1h of the operating method of Example 1 above are applied to the quinolone obtained. A solid is obtained (m.p. 220-221 °C).
IR (KBr): 1611; 1655; 1725 cm^{-1}.
NMR ^1H (DMSO-d6, δ): 0.87 (t, 3H); 0.96 (t, 3H); 1.49 (q, 2H); 1.67 (q, 2H); 1.86 (q, 2H); 3.05 (d, 1H); 3.19 (t, 2H); 3.49 (d, 1H); 5.28 (s, 2H); 5.40 (d, 1H); 5.54 (d, 1H); 6.05 (s, 1H); 7.39 (s, 1H); 7.72 (t, 1H); 7.85 (t, 1H); 8.14 (d, 1H); 8.26 (d, 1H).

Example 6: (5*R*)-5,12-diethyl-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione.

2-aminobenzonitrile is treated with ethylmagnesium bromide according to a procedure similar to Stage 4a and the resulting amino-ketone is treated according to a procedure similar to Stage 4b. Stages 1f to 1h of the operating method of Example 1 above are applied to the quinolone obtained. A solid is obtained (m.p. > 280°C).
IR (KBr): 1652, 1758, 3329 cm^{-1}.
NMR ^1H (DMSO-d6, δ): 0.85 (t, 3H); 1.31 (t, 3H); 1.87 (q, 2H); 3.04 (d, 1H); 3.24 (q, 2H); 3.54 (d, 1H); 5.25 (s, 2H); 5.36 (d, 1H); 5.53 (d, 1H); 6.06 (s, 1H); 7.39 (s, 1H); 7.72 (t, 1H); 7.85 (t, 1H); 8.15 (d, 1H); 8.28 (d, 1H).

Example 7: (5*R*)-5-ethyl-5-hydroxy-12-phenyl-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione.

2-aminophenyl-phenylmethanone is treated according to a procedure similar to Stage 4b. Stages 1f to 1h of the operating method of Example 1 are applied to the quinolone obtained. A solid is obtained (m.p. > 250 °C).

NMR ^{1}H (DMSO-d6, δ): 0.86 (t, 3H); 1.85 (q, 2H); 3.05 (d, 1H); 3.49 (d, 1H); 5.09 (s, 2H); 5.38 (d, 1H); 5.50 (d, 1H); 6.07 (s, 1H); 7.45 (s, 1H); 7.60 – 7.75 (m, 6H); 7.82 (d, 1H); 7.90 (t, 1H); 8.25 (d, 1H).

Example 8: (5*R*)-12-cyclohexyl-5-ethyl-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione.

2-aminobenzonitrile is treated with cyclohexylmagnesium chloride according to a procedure similar to Stage 4a and the resulting amino-ketone is treated according to a procedure similar to that of Stage 4b. Stages 1f to 1h of the operating method of Example 1 above are applied to the quinolone obtained. A solid is obtained (m.p. > 250 °C).

IR (KBr): 1655, 1728, 3500 cm^{-1}.

NMR ^{1}H (DMSO-d6, δ): 0.86 (t, 3H); 1.42 (t, 1H); 1.59 (t, 2H); 1.84 (m, 9H); 3.04 (d, 1H); 3.48 (d, 1H); 3.69 (m, 1H); 5.39 (d, 1H); 5.40 (s, 2H); 5.53 (d, 1H); 6.06 (s, 1H); 7.38 (s, 1H); 7.70 (t, 1H); 7.83 (t, 1H); 8.13 (d, 1H); 8.37 (s, 1H).

Example 9: (5*R*)-5-ethyl-5-hydroxy-12-(4-methylphenyl)-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione.

2-aminophenyl-4-methylphenylmethanone is treated according to a procedure similar to Stage 4b. Stages 1f to 1h of the operating method of Example 1 above are applied to the quinolone obtained. A solid is obtained (m.p. > 280 °C).

IR (KBr): 1655, 1754, 3407 cm^{-1}.

NMR ^{1}H (DMSO-d6, δ): 0.87 (t, 3H); 1.87 (q, 2H); 2.47 (s, 3H); 3.07 (d, 1H); 3.48 (d, 1H); 5.07 (d, 2H); 5.39 (d, 1H); 5.49 (d, 1H); 6.04 (s, 1H); 7.45 (s, 1H); 7.48 (m, 2H); 7.54 (m, 2H); 7.65 (m, 1H); 7.85 (m, 2H); 8.22 (d, 1H).

Example 10: (5*R*)-10-chloro-5-ethyl-12-(2-fluorophenyl)-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione.

2-amino-5-chlorophenyl-2-fluorophenylmethanone is treated according to a procedure similar to that of Stage 4b. Stages 1f to 1h of the operating method of Example 1 above are applied to the quinolone obtained. A solid is obtained (m.p. > 250 °C).
IR (KBr): 1656, 1744, 3397 cm^{-1}.
NMR ^1H (DMSO-d6, δ): 0.86 (t, 3H); 1.85 (q, 2H); 3.06 (d, 1H); 3.47 (d, 1H); 4.93 (d, 1H); 5.17 (d, 1H); 5.37 (d, 1H); 5.49 (d, 1H); 6.05 (s, 1H); 7.46 (s, 1H); 7.50 – 7.65 (m, 3H); 7.65 – 7.80 (m, 2H); 7.91 (d, 1H); 8.27 (d, 1H).

Example 11: (5*R*)-5-ethyl-9,10-difluoro-5-hydroxy-12-phenyl-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione

Stage 11a: 6,7-difluoro-2-phenyl-4*H*-benzo[d][3.1]oxazine-4-one.

A mixture of 2-amino-4,5-difluorobenzoic acid (3.46 g; 20 mmol) and benzoyl chloride (56 ml; 480 mmol) is taken to reflux for 16 hours, then poured into a saturated aqueous solution of sodium bicarbonate (200 ml) and agitated at 80°C for 2 hours. The resulting mixture is extracted with dichloromethane (2 x 100 ml). The combined extracts are washed with water and with a saturated solution of sodium chloride, then dried over magnesium sulphate and concentrated under reduced pressure. The residue is taken up in ethyl ether and the precipitate thus formed is recovered by filtration, washed with ethyl ether, and dried under reduced pressure to produce 3.2 g of a white solid (m.p.: 154°C).
IR (KBr): 1613, 1657, 3341, 3467 cm^{-1}.
NMR ^1H (DMSO-d6, δ): 7.5-7.8 (m, 3H); 7.8-7.9 (m, 1H); 8.1-8.3 (m, 1H).

Stage 11b: 2-benzoyl-4,5-difluoro-1-phenylcarboxamidobenzene.

A suspension of benzoxazine (obtained according to Stage 11a; 6.78 g; 26 mmol) in dichloromethane (260 ml) is treated dropwise under argon at –78°C with phenylmagnesium bromide (3M in ethyl ether; 22 ml; 66 mmol). The resulting mixture is agitated at –78°C for 1 hour, then hydrolyzed by adding a saturated aqueous solution of ammonium chloride (200 ml) and extracted with dichloromethane (2 x 100 ml). The combined extracts are washed with water and with a saturated aqueous solution of sodium chloride, then dried over magnesium sulphate and concentrated under reduced pressure. The residue taken up in isopropyl ether produces whites crystals which are recovered by filtration and dried . 7.3 g of product is obtained (m.p.: 58-59°C).
IR (KBr): 1423, 1537, 1599, 1682 cm^{-1}.
NMR ^1H (DMSO-d6, δ): 7.4-7.6 (m, 9H); 7.69 (d, 2H); 7.88 (dd, 1H).

Stage 11c: 2-amino-4,5-difluorophenyl-phenylmethanone.

A solution of *N*-benzoylated amino-ketone (obtained according to Stage 11b; 7.3 g; 21.7 mmol) in glacial acetic acid (300 ml) is treated with hydrobromic acid at 48% (150 ml) and the reaction medium is taken to reflux for 10 hours. After cooling down to ambient temperature, the resulting mixture is concentrated under reduced pressure, then taken up in a saturated aqueous solution of sodium bicarbonate (200 ml) and extracted with ethyl acetate (2 x 100 ml). The combined extracts are washed with water and with a saturated aqueous solution of sodium chloride, then dried over magnesium sulphate and concentrated under reduced pressure. The residue is taken up with pentane and the precipitate thus formed is recovered by filtration to produce 4 g of a light yellow solid (m.p.: 100-101 °C).
IR (KBr):1514, 1563, 1645, 3372, 3482 cm^{-1}.
NMR ^1H (DMSO-d6, δ): 6.83 (dd, 1H); 7.1-7.4 (m, 3H); 7.5-7.7 (m, 5H).

Stage 11d: (5*R*)-5-ethyl-9,10-difluoro-5-hydroxy-12-phenyl-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione.

The aminoketone obtained in Stage 11c is treated according to a procedure similar to that of Stage 4b. Stages 1f to 1h of the operating method of Example 1 above are applied to the quinolone obtained. A solid is obtained (m.p. > 250 °C).
IR (KBr):1659, 1734, 3386 cm^{-1}.
NMR ^1H (DMSO-d6, δ): 0.85 (t, 3H); 1.80 (q, 2H); 3.06 (d, 1H); 3.45 (d, 1H); 5.00 (d, 1H); 5.35 (d, 1H); 5.48 (d, 1H); 6.03 (s, 1H); 7.39 (s, 1H); 7.55-7.75 (m, 6H); 8.24 (dd, 1H).

Example 12: (5*R*)-5-ethyl-9-fluoro-5-hydroxy-12-phenyl-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione.

2-amino-4-fluorobenzoic acid is treated according to a procedure similar to Stages 11a to 11c and the resulting aminoketone is treated according to a procedure similar to Stage 4b. Stages 1f to 1h of the operating method of Example 1 above are applied to the quinolone obtained. A solid is obtained (m.p. > 250 °C).
NMR ^1H (DMSO-d6, δ): 0.86 (t, 3H); 1.84 (q, 2H); 3.06 (d, 1H); 3.46 (d, 1H); 5.00 (d, 1H); 5.08 (d, 1H); 5.37 (d, 1H); 5.49 (d, 1H); 6.03 (s, 1H); 7.43 (s, 1H); 7.50 – 7.80 (m, 6H); 7.85 (t, 1H); 7.96 (d, 1H).

Example 13: (5*R*)-12-butyl-5-ethyl-9,10-difluoro-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione

Stage 13a: *N*-(3,4-difluorophenyl)acetamide.

A mixture of 3,4-difluoroaniline (50 ml; 500 mmol) and triethylamine (70 ml; 500 mmol) in dichloromethane (1.5 l) is cooled down using an ice bath. Acetic anhydride (71.5 ml; 750 mmol) is added dropwise and the reaction mixture is agitated for 1 hour at ambient temperature. The mixture obtained is then washed sequentially with water, with a solution of sodium bicarbonate at 10%, and with a saturated aqueous solution of sodium chloride. The organic fraction, dried over sodium sulphate, is concentrated under reduced pressure. The residue is suspended in pentane, filtered and dried under reduced pressure in order to produce the expected anilide, a beige solid (m.p.: 126-127.5 °C).

NMR ^{1}H (DMSO-d6, δ): 2.15 (s, 3H); 7.10-7.65 (m, 2H); 7.65-8.10 (m, 1H); 10.30 (broad peak, 1H).

Stage 13b: 2-chloro-6,7-difluoro-3-quinolinecarbaldehyde.

The acetanilide obtained according to Stage 13a (32 g; 220 mmol) is added to a Vilsmeyer's reagent obtained under argon with anhydrous *N,N*-dimethylformamide (34 ml; 440 mmol) cooled down using an ice bath, treated dropwise with phosphorus oxychloride (103 ml; 1.1 mol), then agitated for 0.5 hours before allowing the temperature to rise to ambient temperature. The mixture thus obtained is agitated at 70°C for 16 hours, then cooled down to ambient temperature. The reaction medium is then poured dropwise into a water-ice mixture (400 ml), and the resulting mixture is agitated for 2 hours. The precipitate obtained is filtered and washed with water until the pH is neutral, then dried under reduced pressure in the presence of phosphorus pentoxide in order to produce a yellow solid (m.p.: 226-229 °C).

IR (KBr): 888, 1061, 1262, 1507, 1691 cm^{-1}.

NMR ^{1}H (DMSO-d6, δ): 8.17 (dd, 1H); 8.39 (dd, 1H); 8.97 (d, 1H); 10.34 (d, 1H).

Stage 13c: 2-chloro-6,7-difluoro-3-quinolylmethanol.

A suspension of quinoline-carbaldehyde obtained according to Stage 13b (9 g; 39 mmol) in methanol (400 ml) is treated with sodium borohydride (2 g; 53 mmol) at ambient temperature for 0.5 h. The excess borohydride is destroyed by acetic acid (2 ml) and the reaction medium is concentrated under reduced pressure. The residue, taken up in ethyl acetate (500 ml), is washed sequentially with an aqueous solution of sodium bicarbonate at 10%, with water, and with a saturated aqueous solution of sodium chloride. The organic phase, dried over magnesium sulphate, is concentrated

under reduced pressure. The residue is recrystallized from 1,2-dichloroethane in order to produce the expected quinolylmethanol, a beige solid (m.p.: 166,5-167°C).
IR (KBr): 871, 1038, 1253, 1513 cm^{-1}.
NMR ^1H (DMSO-d6, δ): 4.67 (d, 2H); 5.80 (t, 1H); 8.01 (dd, 1H); 8.22 (dd, 1H); 8.48 (s, 1H).

Stage 13d: (5*R*)-5-ethyl-9,10-difluoro-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione.

The quinolylmethanol obtained in Stage 13c is treated with (+)-EHHOPD according to the procedure in Stage 1h. A white solid is obtained.
IR (KBr): 871, 1261, 1512, 1579, 1654, 1746 cm^{-1}.
NMR ^1H (DMSO-d6, δ): 0.87 (t, 3H); 1.85 (m, 2H); 3.08 (d, 1H); 3.44 (d, 1H); 5.26 (s, 2H); 5.39 (d, 2H); 5.52 (d, 1H); 5.99 (s, 1H); 7.39 (s, 1H); 8.15 (dd, 1H); 8.23 (dd, 1H); 8.68 (s, 1H).

Stage 13e: (5*R*)-12-butyl-5-ethyl-9,10-difluoro-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione.

The product of Stage 13d (100 mg; 0.25 mmol) is dissolved in a mixture of water (1.33 ml) and sulphuric acid at 95% (1 ml). Heptahydrated iron (III) sulphate (28 mg; 0.10 mmol); valeraldehyde (0.17 ml; 1.60 mmol) are added to this solution and the resulting solution is cooled down with an ice bath. The reaction medium is then treated dropwise with hydrogen peroxide at 30% (0.38 ml; 1 mmol); agitated for 5 hours at ambient temperature, then diluted with water (50 ml) and extracted with dichloromethane (4 x 50 ml). The combined extracts are washed with water and with a saturated aqueous solution of sodium chloride, then dried over magnesium sulphate and concentrated under reduced pressure. The residue is purified by chromatography at medium pressure (SiO_2, $MeOH/CH_2Cl_2$, 5/95) in order to produce the expected solid (m.p. > 275 °C).
IR (KBr): 1656, 1748, 3385 cm^{-1}.
NMR ^1H (DMSO-d6, δ): 0.85 (t, 3H); 0.94 (t, 3H); 1.47 (q, 2H); 1.64 (m, 2H); 1.83 (q, 2H); 3.05 (d, 1H); 3.16 (m, 2H); 3.47 (d, 1H); 5.27 (s, 2H); 5.39 (d, 1H); 5.52 (d, 1H); 6.05 (s, 1H); 7.35 (s, 1H); 8.13 (m, 1H); 8.32 (m, 1H).

<u>Example 14:</u> (5*R*)-12-benzyl-5-ethyl-9,10-difluoro-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione.

The product of Stage 13d is treated with phenylacetaldehyde according to a procedure similar to that of Stage 13e in order to produce the expected solid (m.p. 275 °C (dec.)).
IR (KBr): 1656, 1707, 1749 cm^{-1}.
NMR ^1H (DMSO-d6, δ): 0.86 (t, 3H); 1.84 (q, 2H); 3.05 (d, 1H); 3.48 (d, 1H); 4.64 (s, 2H); 5.19 (d, 2H); 5.38 (d, 1H); 5.51 (d, 1H); 6.06 (s, 1H); 7.20 (m, 1H); 7.26 (m, 4H); 7.37 (s, 1H); 8.15 (t, 1H); 8.31 (t, 1H).

Example 15: (5*R*)-5-ethyl-9,10-difluoro-5-hydroxy-12-propyl-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione.

The product of Stage 13d is treated with butyraldehyde according to a procedure similar to that of Stage 13e in order to produce the expected solid (m.p. 250°C).
IR (KBr): 1656, 3425 cm^{-1}.
NMR ^1H (DMSO-d6, δ): 0.86 (t, 3H); 1.04 (t, 3H); 1.70 (q, 2H); 1.84 (q, 2H); 3.07 (d, 1H); 3.15 (t, 2H); 3.46 (d, 1H); 5.25 (s, 1H); 5.39 (d, 1H); 5.52 (d, 1H); 6.02 (s, 1H); 7.36 (s, 1H); 8.12 (m, 1H); 8.34 (m, 1H).

Example 16: (5*R*)-5,12-diethyl-9,10-difluoro-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione.

The product of Stage 13d is treated with propionaldehyde according to a procedure similar to that in Stage 13e in order to produce the expected solid (m.p. > 275°C).
IR (KBr): 1656, 1725, 3308 cm^{-1}.
NMR ^1H (DMSO-d6, δ): 0.85 (t, 3H); 1.28 (t, 3H); 1.83 (q, 2H); 3.05 (d, 1H); 3.19 (q, 2H), 3.47 (d, 1H); 5.29 (s, 2H); 5.39 (d, 1H); 5.52 (d, 1H); 6.06 (s, 1H); 7.36 (s, 1H); 8.15 (m, 1H); 8.35 (m, 1H).

Example 17: (5*R*)-5-ethyl-9,10-difluoro-5-hydroxy-12-(2-trimethylsilylethyl)-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione.

The product of Stage 13d is treated with 3-trimethylsilylpropanal (obtained according to Sarkar, T. K., et al., *Tetrahedron* (1990), vol. **46**, p. 1885) according to a procedure similar to Stage 13e in order to produce the expected solid (m.p. 276°C).
NMR ^1H (DMSO-d6, δ): 0.14 (s, 9H); 0.86 (m, 5H); 1.83 (q, 2H); 3.07 (m, 3H); 3.46 (d, 1H); 5.26 (s, 2H); 5.40 (d, 1H); 5.51 (d, 1H); 6.06 (s, 1H); 7.34 (s, 1H); 8.14 (m, 2H).

Example 18: (5*R*)-5-ethyl-9,11-difluoro-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione.

The operation is carried out with 3,5-difluoroaniline according to Stages 13a to 13c and the quinolylmethanol thus obtained is treated with (+)-EHHOPD according to the procedure of Stage 1h. A white solid is obtained (m.p. 227 °C (dec.)).
IR (KBr): 1638, 1748, 3310 cm^{-1}.
NMR ^1H (DMSO-d6, δ): 0.87 (t, 3H); 1.85 (q, 2H); 3.07 (d, 1H); 3.46 (d, 1H); 5.26 (s, 2H); 5.40 (d, 1H); 5.52 (d, 1H); 6.03 (s, 1H); 7.42 (s, 1H); 7.70 (t, 1H); 7.80 (d, 1H); 8.82 (s, 1H).

Example 19: (5*R*)-12-butyl-5-ethyl-9,11-difluoro-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione.

The product of Example 18 is treated with valeraldehyde according to a procedure similar to that of Stage 13e in order to produce the expected solid (m.p. 190 °C).
IR (KBr): 1657, 1751, 3385 cm^{-1}.
NMR ^1H (DMSO-d6, δ): 0.86 (t, 3H); 0.96 (t, 3H); 1.49 (q, 2H); 1.66 (q, 2H); 1.84 (q, 2H); 3.07 (d, 1H); 3.46 (d, 1H); 5.30 (s, 2H); 5.40 (d, 1H); 5.53 (d, 1H); 6.03 (s, 1H); 7.39 (s, 1H); 7.67 (t, 1H); 7.78 (d, 1H).

Example 20: (5*R*)-5,12-diethyl-9,11-difluoro-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione.

The product of Example 18 is treated with propionaldehyde according to a procedure similar to that in Stage 13e to produce the expected solid (m.p. 255°C).
NMR ^1H (DMSO-d6, δ): 0.86 (t, 3H); 1.33 (t, 3H); 1.84 (q, 2H); 3.06 (d, 1H); 3.29 (m, 2H); 3.57 (d, 1H); 5.28 (s, 2H); 5.35 (d, 1H); 5.53 (d, 1H); 6.04 (s, 1H); 7.38 (s, 1H); 7.69 (m, 1H); 7.80 (m, 1H).

Example 21: (5*R*)-5-ethyl-5-hydroxy-12-propyl-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione.

(5*R*)-5-ethyl-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino [1,2-*b*]quinoline-3,15-dione (obtained according to the procedure described in the PCT Patent Application WO 97/00876) is treated with butyraldehyde according to a procedure similar to that of Stage 13e in order to produce the expected solid (m.p. 265 °C (dec.)).
IR (KBr): 1590, 1653, 3287 cm^{-1}.
NMR ^1H (DMSO-d6, δ): 0.87 (t, 3H); 1.06 (t, 3H); 1.73 (q, 2H); 1.82 (q, 2H); 3.06 (d, 1H); 3.19 (t, 2H); 3.48 (d, 1H); 5.24 (s, 2H); 5.31 (d, 1H); 5.54 (d, 1H); 6.02 (s, 1H); 7.38 (s, 1H); 7.72 (t, 1H); 7.85 (t, 1H); 8.15 (d, 1H); 8.28 (d, 1H).

Example 22: (5*R*)-5-ethyl-5-hydroxy-12-(2-trimethylsilylethyl)-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione.

(5*R*)-5-ethyl-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino [1,2-*b*]quinoline-3,15-dione (obtained according to the procedure described in the PCT Patent Application WO 97/00876) is treated with 3-trimethylsilylpropanal (obtained according to Sarkar, T. K., et al., *Tetrahedron* (1990), vol.**46**, p. 1885) according to a procedure similar to that of Stage 13e in order to produce the expected solid (m.p. > 250°C).

IR (KBr): 1655, 1753, 3420 cm^{-1}.

NMR ^1H (DMSO-d6, δ): 0.11 (s, 9H); 0.88 (t, 3H); 0.91 (m, 2H); 1.89 (q, 2H); 3.07 (d, 1H); 3.12 (m, 2H); 3.47 (d, 1H); 5.25 (s, 2H); 5.33 (d, 1H); 5.41 (d, 1H); 5.54 (d, 1H); 6.02 (s, 1H); 7.39 (s, 1H); 7.73 (t, 1H); 7.82 (t, 1H); 8.15 (s, 1H).

Example 23: (5*R*)-12-butyl-5-ethyl-9-fluoro-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione.

The product of Example 2 is treated with valeraldehyde according to a procedure similar to Stage 13e to produce the expected solid (m.p. 235-236°C).

NMR ^1H (DMSO-d6, δ): 0.86 (t, 3H); 0.95 (t, 3H); 1.48 (m, 2H); 1.67 (m, 2H); 1.85 (q, 2H); 3.06 (d, 1H); 3.20 (t, 2H); 3.46 (d, 1H); 5.27 (s, 2H); 5.40 (d, 1H); 5.53 (d, 1H); 6.02 (s, 1H); 7.38 (s, 1H); 7.64 (t, 1H); 7.87 (d, 1H); 8.36 (dd, 1H).

Example 24: (5*R*)-5,12-diethyl-9-fluoro-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione.

The product of Example 2 is treated with propionaldehyde according to a procedure similar to Stage 13e in order to produce the expected solid.

NMR ^1H (DMSO-d6, δ): 0.86 (t, 3H); 1.31 (t, 3H); 1.85 (q, 2H); 3.06 (d, 1H); 3.22 (q, 2H); 3.47 (d, 1H); 5.24 (s, 2H); 5.39 (d, 1H); 5.53 (d, 1H); 6.03 (s, 1H); 7.38 (s, 1H); 7.64 (t, 1H); 7.87 (d, 1H); 8.37 (dd, 1H).

Example 25: (5*R*)-5-Ethyl-5-hydroxy-12-isopentyl-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione.

2-aminobenzonitrile is treated with isopentylmagnesium bromide according to a procedure similar to Stage 4a and the resulting amino-ketone is treated according to a

procedure similar to Stage 4b. Stages 1f to 1h of the operating method of Example 1 above are applied to the quinolone obtained. A solid is obtained (m.p. 263 °C).
IR (KBr): 1655, 1743, 3343 cm^{-1}.
NMR ^1H (DMSO-d6, δ): 0.85 (t, 3H); 1.00 (d, 6H); 1.54 (m, 2H); 1.79 (m, 1H); 1.82 (m, 2H); 3.06 (4, 1H); 3.14 (m, 2H); 3.45 (d, 1H); 5.20 (s, 2H); 5.38 (d, 1H); 5.52 (d, 1H); 5.99 (s, 1H); 7.37 (s, 1H); 7.70 (t, 1H); 7.82 (t, 1H); 8.12 (d, 1H); 8.19 (d, 1H).

Example 26: (5*R*)-5-ethyl-12-(4-fluorophenyl)-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione.

2-aminobenzonitrile is treated by 4-fluorophenylmagnesium bromide according to a procedure similar to Stage 4a and the resulting amino-ketone is treated according to a procedure similar to Stage 4b. Stages 1f to 1h of the operating method of Example 1 above are applied to the quinolone obtained.

Example 27: (5*R*)-12-(2,6-difluorophenyl)-5-ethyl-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione.

2-aminobenzonitrile is treated by 2,6-difluorophenylmagnesium bromide according to a procedure similar to Stage 4a and the resulting amino-ketone is treated according to a procedure similar to Stage 4b. Stages 1f to 1h of the operating method of Example 1 above are applied to the quinolone obtained.

Example 28: (5*R*)-12-(3,5-difluorophenyl)-5-ethyl-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione.

2-aminobenzonitrile is treated with 3,5-difluorophenylmagnesium bromide according to a procedure similar to Stage 4a and the resulting amino-ketone is treated according to a procedure similar to Stage 4b. Stages 1f to 1h of the operating method of Example 1 above are applied to the quinolone obtained.

Example 29: (5*R*)-5-ethyl-5-hydroxy-12-(3,4,5-trifluorophenyl)-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione.

2-aminobenzonitrile is treated with 3,4,5-trifluorophenylmagnesium bromide according to a procedure similar to Stage 4a and the resulting amino-ketone is treated according to a procedure similar to Stage 4b. Stages 1f to 1h of the operating method of Example 1 above are applied to the quinolone obtained.

Example 30: **(5*R*)-5-ethyl-5-hydroxy-12-(2,4,6-trifluorophenyl)-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione.**

2-aminobenzonitrile is treated with 2,4,6-trifluorophenylmagnesium bromide according to a procedure similar to Stage 4a and the resulting amino-ketone is treated according to a procedure similar to Stage 4b. Stages 1f to 1h of the operating method of Example 1 above are applied to the quinolone obtained.

Example 31: **(5*R*)-5-ethyl-5-hydroxy-12-(2,3,5,6-tetrafluorophenyl)-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione.**

2-aminobenzonitrile is treated with 2,3,5,6-tetrafluorophenylmagnesium bromide according to a procedure similar to Stage 4a and the resulting amino-ketone is treated according to a procedure similar to Stage 4b. Stages 1f to 1h of the operating method of Example 1 above are applied to the quinolone obtained.

Example 32: **(5*R*)-5-ethyl-5-hydroxy-12-(2,3,4,5,6-pentafluorophenyl)-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione.**

2-aminobenzonitrile is treated with 2,3,4,5,6-pentafluorophenylmagnesium bromide according to a procedure similar to Stage 4a and the resulting amino-ketone is treated according to a procedure similar to Stage 4b. Stages 1f to 1h of the operating method of Example 1 above are applied to the quinolone obtained.

Example 33: **(5*R*)-5-ethyl-9-fluoro-12-(4-fluorophenyl)-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione.**

2-amino-4-fluorobenzoic acid is treated according to a procedure similar to Stages 11a to 11c using 4-fluorophenylmagnesium bromide of Stage 11b, and the resulting amino-ketone is treated according to a procedure similar to Stage 4b. Stages 1f to 1h of the operating method of Example 1 above are applied to the quinolone obtained.

Example 34: **(5*R*)-12-(2,6-difluorophenyl)-5-ethyl-9-fluoro-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione.**

2-amino-4-fluorobenzoic acid is treated according to a procedure similar to Stages 11a to 11c using 2,6-difluorophenylmagnesium bromide of Stage 11b, and the resulting amino-ketone is treated according to a procedure similar to Stage 4b. Stages 1f to 1h of the operating method of Example 1 above are applied to the quinolone obtained.

Example 35: (5*R*)-12-(3,5-difluorophenyl)-5-ethyl-9-fluoro-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione.

2-amino-4-fluorobenzoic acid is treated according to a procedure similar to Stages 11a to 11c using 3,5-difluorophenylmagnesium bromide of Stage 11b, and the resulting amino-ketone is treated according to a procedure similar to Stage 4b. Stages 1f to 1h of the operating method of Example 1 above are applied to the quinolone obtained.

Example 36: (5*R*)-5-ethyl-9-fluoro-5-hydroxy-12-(3,4,5-trifluorophenyl)-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione.

2-amino-4-fluorobenzoic acid is treated according to a procedure similar to Stages 11a to 11c using 3,4,5-trifluorophenylmagnesium bromide of Stage 11b and the resulting amino-ketone is treated according to a procedure similar to Stage 4b. Stages 1f to 1h of the operating method of Example 1 above are applied to the quinolone obtained.

Example 37: (5*R*)-5-ethyl-9-fluoro-5-hydroxy-12-(2,4,6-trifluorophenyl)-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione.

2-amino-4-fluorobenzoic acid is treated according to a procedure similar to Stages 11a to 11c using 2,4,6-trifluorophenylmagnesium bromide of Stage 11b, and the resulting amino-ketone is treated according to a procedure similar to Stage 4b. Stages 1f to 1h of the operating method of Example 1 above are applied to the quinolone obtained.

Example 38: (5*R*)-5-ethyl-9-fluoro-5-hydroxy-12-(2,3,5,6-tetrafluorophenyl)-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione.

2-amino-4-fluorobenzoic acid is treated according to a procedure similar to Stages 11a to 11c using 2,3,5,6-tetrafluorophenylmagnesium bromide of Stage 11b, and the resulting amino-ketone is treated according to a procedure similar to Stage 4b. Stages 1f to 1h of the operating method of Example 1 above are applied to the quinolone obtained.

Example 39: (5*R*)-5-ethyl-9-fluoro-5-hydroxy-12-(2,3,4,5,6-pentafluorophenyl)-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione.

2-amino-4-fluorobenzoic acid is treated according to a procedure similar to Stages 11a to 11c using 2,3,4,5,6-pentafluorophenylmagnesium bromide of Stage 11b, and the resulting amino-ketone is treated according to a procedure similar to Stage 4b. Stages 1f

to 1h of the operating method of Example 1 above are applied to the quinolone obtained.

Example 40: **(5*R*)-5-ethyl-9,10-difluoro-12-(4-fluorophenyl)-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione.**

2-amino-4,5-difluorobenzoic acid is treated according to a procedure similar to Stages 11a to 11c using 4-fluorophenylmagnesium bromide of Stage 11b, and the resulting amino-ketone is treated according to a procedure similar to Stage 4b. Stages 1f to 1h of the operating method of Example 1 above are applied to the quinolone obtained.

Example 41: **(5*R*)-12-(2,6-difluorophenyl)-5-ethyl-9,10-difluoro-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione.**

2-amino-4,5-difluorobenzoic acid is treated according to a procedure similar to Stages 11a to 11c using 2,6-difluorophenylmagnesium bromide of Stage 11b, and the resulting amino-ketone is treated according to a procedure similar to Stage 4b. Stages 1f to 1h of the operating method of Example 1 above are applied to the quinolone obtained.

Example 42: **(5*R*)-12-(3,5-difluorophenyl)-5-ethyl-9,10-difluoro-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione.**

2-amino-4,5-difluorobenzoic acid is treated according to a procedure similar to Stages 11a to 11c using 3,5-difluorophenylmagnesium bromide of Stage 11b, and the resulting amino-ketone is treated according to a procedure similar to Stage 4b. Stages 1f to 1h of the operating method of Example 1 above are applied to the quinolone obtained.

Example 43: **(5*R*)-5-ethyl-9,10-difluoro-5-hydroxy-12-(3,4,5-trifluorophenyl)-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione.**

2-amino-4,5-difluorobenzoic acid is treated according to a procedure similar to Stages 11a to 11c using 3,4,5-trifluorophenylmagnesium bromide of Stage 11b, and the resulting amino-ketone is treated according to a procedure similar to Stage 4b. Stages 1f to 1h of the operating method of Example 1 above is applied to the quinolone obtained.

Example 44: **(5*R*)-5-ethyl-9,10-difluoro-5-hydroxy-12-(2,4,6-trifluorophenyl)-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione.**

2-amino-4,5-difluorobenzoic acid is treated according to a procedure similar to Stages 11a to 11c using 2,4,6-trifluorophenylmagnesium bromide of Stage 11b, and the resulting amino-ketone is treated according to a procedure similar to Stage 4b. Stages 1f to 1h of the operating method of Example 1 above are applied to the quinolone obtained.

Example 45: (5*R*)-5-ethyl-9,10-difluoro-5-hydroxy-12-(2,3,5,6-tetrafluorophenyl)-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione.

2-amino-4,5-difluorobenzoic acid is treated according to a procedure similar to Stages 11a to 11c using 2,3,5,6-tetrafluorophenylmagnesium bromide of Stage 11b, and the resulting amino-ketone is treated according to a procedure similar to Stage 4b. Stages 1f to 1h of the operating method of Example 1 above are applied to the quinolone obtained.

Example 46: (5*R*)-5-ethyl-9,10-difluoro-5-hydroxy-12-(2,3,4,5,6-pentafluorophenyl)-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione.

2-amino-4,5-difluorobenzoic acid is treated according to a procedure similar to Stages 11a to 11c using 2,3,4,5,6-pentafluorophenylmagnesium bromide of Stage 11b, and the resulting amino-ketone is treated according to a procedure similar to Stage 4b. Stages 1f to 1h of the operating method of Example 1 above are applied to the quinolone obtained.

Example 47: (5*R*)-5-ethyl-9,11-difluoro-12-(4-fluorophenyl)-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione.

2-amino-4,6-difluorobenzoic acid is treated according to a procedure similar to Stages 11a to 11c using 4-fluorophenylmagnesium bromide of Stage 11b, and the resulting amino-ketone is treated according to a procedure similar to Stage 4b. Stages 1f to 1h of the operating method of Example 1 above are applied to the quinolone obtained.

Example 48: (5*R*)-12-(2,6-difluorophenyl)-5-ethyl-9,11-difluoro-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione.

2-amino-4,6-difluorobenzoic acid is treated according to a procedure similar to Stages 11a to 11c using 2,6-difluorophenylmagnesium bromide of Stage 11b, and the resulting

amino-ketone is treated according to a procedure similar to Stage 4b. Stages 1f to 1h of the operating method of Example 1 above are applied to the quinolone obtained.

Example 49: (5*R*)-12-(3,5-difluorophenyl)-5-ethyl-9,11-difluoro-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione.

2-amino-4,6-difluorobenzoic acid is treated according to a procedure similar to Stages 11a to 11c using 3,5-difluorophenylmagnesium bromide of Stage 11b, and the resulting amino-ketone is treated according to a procedure similar to Stage 4b. Stages 1f to 1h of the operating method of Example 1 above are applied to the quinolone obtained.

Example 50: (5*R*)-5-ethyl-9,11-difluoro-5-hydroxy-12-(3,4,5-trifluorophenyl)-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione.

2-amino-4,6-difluorobenzoic acid is treated according to a procedure similar to Stages 11a to 11c using 3,4,5-trifluorophenylmagnesium bromide of Stage 11b, and the resulting amino-ketone is treated according to a procedure similar to Stage 4b. Stages 1f to 1h of the operating method of Example 1 above are applied to the quinolone obtained.

Example 51: (5*R*)-5-ethyl-9,11-difluoro-5-hydroxy-12-(2,4,6-trifluorophenyl)-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione.

2-amino-4,6-difluorobenzoic acid is treated according to a procedure similar to Stages 11a to 11c using 2,4,6-trifluorophenylmagnesium bromide of Stage 11b, and the resulting amino-ketone is treated according to a procedure similar to Stage 4b. Stages 1f to 1h of the operating method of Example 1 above are applied to the quinolone obtained.

Example 52: (5*R*)-5-ethyl-9,11-difluoro-5-hydroxy-12-(2,3,5,6-tetrafluorophenyl)-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione.

2-amino-4,6-difluorobenzoic acid is treated according to a procedure similar to Stages 11a to 11c using 2,3,5,6-tetrafluorophenylmagnesium bromide of Stage 11b, and the resulting amino-ketone is treated according to a procedure similar to Stage 4b. Stages 1f to 1h of the operating method of Example 1 above are applied to the quinolone obtained.

Example 53: (5*R*)-5-ethyl-9,11-difluoro-5-hydroxy-12-(2,3,4,5,6-pentafluorophenyl)-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione.

2-amino-4,6-difluorobenzoic acid is treated according to a procedure similar to Stages 11a to 11c using 2,3,4,5,6-pentafluorophenylmagnesium bromide of Stage 11b, and the resulting amino-ketone is treated according to a procedure similar to Stage 4b. Stages 1f to 1h of the operating method of Example 1 above are applied to the quinolone obtained.

Example 54: (5*R*)-5-ethyl-9-fluoro-5-hydroxy-12-propyl-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione.

The product of Example 2 is treated with butyraldehyde according to a procedure similar to Stage 13e in order to produce the expected solid.

Example 55: (5*R*)-5-ethyl-9-fluoro-5-hydroxy-12-(3,3,3-trifluoropropyl)-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione.

The product of Example 2 is treated with 4,4,4-trifluorobutyraldehyde according to a procedure similar to Stage 13e in order to produce the expected solid.

Example 56: (5*R*)-5-ethyl-9-fluoro-5-hydroxy-12-isopentyl-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione.

The product of Example 2 is treated with 4-methylpentanal according to a procedure similar to Stage 13e in order to produce the expected solid.

Example 57: (5*R*)-5-ethyl-9-fluoro-5-hydroxy-12-pentyl-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione.

The product of Example 2 is treated with hexanal according to a procedure similar to Stage 13e in order to produce the expected solid.

Example 58: (5*R*)-5-ethyl-9-fluoro-5-hydroxy-12-phenethyl-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione.

The product of Example 2 is treated with 3-phenylpropanal according to a procedure similar to Stage 13e in order to produce the expected solid.

Example 59: (5*R*)-12-decyl-5-ethyl-9-fluoro-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione.

The product of Example 2 is treated with undecanal according to a procedure similar to Stage 13e in order to produce the expected solid.

Example 60: (5*R*)-12-(2-cyclohexylethyl)-5-ethyl-9-fluoro-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione.

The product of Example 2 is treated with 3-cyclohexylpropanal according to a procedure similar to Stage 13e in order to produce the expected solid.

Example 61: (5*R*)-12-(3,3-dimethylbutyl)-5-ethyl-9-fluoro-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione.

The product of Example 2 is treated with 4,4-dimethylpentanal according to a procedure similar to Stage 13e in order to produce the expected solid.

Example 62: (5*R*)-5-ethyl-9,10-difluoro-5-hydroxy-12-propyl-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione.

The product of Stage 13d is treated with butyraldehyde according to a procedure similar to Stage 13e in order to produce the expected solid.

Example 63: (5*R*)-5-ethyl-9,10-difluoro-5-hydroxy-12-(3,3,3-trifluoropropyl)-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione.

The product of Stage 13d is treated with 4,4,4-trifluorobutyraldehyde according to a procedure similar to Stage 13e in order to produce the expected solid.

Example 64: (5*R*)-5-ethyl-9,10-difluoro-5-hydroxy-12-isopentyl-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione.

The product of Stage 13d is treated with 4-methylpentanal according to a procedure similar to Stage 13e in order to produce the expected solid.

Example 65: (5*R*)-5-ethyl-9,10-difluoro-5-hydroxy-12-pentyl-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione.

The product of Stage 13d is treated with hexanal according to a procedure similar to Stage 13e in order to produce the expected solid.

Example 66: (5*R*)-5-ethyl-9,10-difluoro-5-hydroxy-12-phenethyl-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione.

The product of Stage 13d is treated with 3-phenylpropanal according to a procedure similar to Stage 13e in order to produce the expected solid.

Example 67: (5*R*)-12-decyl-5-ethyl-9,10-difluoro-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione.

The product of Stage 13d is treated with undecanal according to a procedure similar to Stage 13e in order to produce the expected solid.

Example 68: (5*R*)-12-(2-cyclohexylethyl)-5-ethyl-9,10-difluoro-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione.

The product of Stage 13d is treated with 3-cyclohexylpropanal according to a procedure similar to Stage 13e in order to produce the expected solid.

Example 69: (5*R*)-12-(3,3-dimethylbutyl)-5-ethyl-9,10-difluoro-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione.

The product of Stage 13d is treated with 4,4-dimethylpentanal according to a procedure similar to Stage 13e in order to produce the expected solid.

Example 70: (5*R*)-5-ethyl-9,11-difluoro-5-hydroxy-12-propyl-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione.

The product of Example 18 is treated with butyraldehyde according to a procedure similar to Stage 13e in order to produce the expected solid.

Example 71: (5*R*)-5-ethyl-9,11-difluoro-5-hydroxy-12-(3,3,3-trifluoropropyl)-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione.

The product of Example 18 is treated with 4,4,4-trifluorobutyraldehyde according to a procedure similar to Stage 13e in order to produce the expected solid.

Example 72: (5*R*)-5-ethyl-9,11-difluoro-5-hydroxy-12-isopentyl-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione.

The product of Example 18 is treated with 4-methylpentanal according to a procedure similar to Stage 13e in order to produce the expected solid.

Example 73: (5*R*)-5-ethyl-9,11-difluoro-5-hydroxy-12-pentyl-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione.

The product of Example 18 is treated with hexanal according to a procedure similar to Stage 13e in order to produce the expected solid.

Example 74: (5*R*)-5-ethyl-9,11-difluoro-5-hydroxy-12-phenethyl-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione.

The product of Example 18 is treated with 3-phenylpropanal according to a procedure similar to Stage 13e in order to produce the expected solid.

Example 75: (5*R*)-12-decyl-5-ethyl-9,11-difluoro-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione.

The product of Example 18 is treated with undecanal according to a procedure similar to Stage 13e in order to produce the expected solid.

Example 76: (5*R*)-12-(2-cyclohexylethyl)-5-ethyl-9,11-difluoro-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione.

The product of Example 18 is treated with 3-cyclohexylpropanal according to a procedure similar to Stage 13e in order to produce the expected solid.

Example 77: (5*R*)-12-(3,3-dimethylbutyl)-5-ethyl-9,11-difluoro-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione.

The product of Example 18 is treated with 4,4-dimethylpentanal according to a procedure similar to Stage 13e in order to produce the expected solid.

PHARMACOLOGICAL STUDY OF THE PRODUCTS OF THE INVENTION

Procedure

Adenocarcinoma HT29 cells from the human colon are cultured in a single layer at 37°C in a humidified atmosphere containing 95% of air and 5% of CO_2, in a modified essential Earle's medium at 4.5 g/l (Gibco, Paisley, United Kingdom); completed with 10% of inactivated foetal calf serum, 2 mM of glutamine, and 50 µg/ml of gentamycin (Gibco, Paisley, United Kingdom).

Approximately 2000 cells are seeded with the culture medium above in the wells of a microplate (96 wells, flat-bottomed) and incubated for 24 hours. Solutions in *N,N*-dimethyl-acetamide (DMA) of each of the examples of the invention, diluted in the culture medium so that the final concentration of DMA is 0.1% (v/v), are added to the plate cultures in order to obtain final concentration ranges from 1×10^{-13} to 1×10^{-5} M, and the cells are incubated for 72 hours.

The WST1 staining reagent, (Boehringer Mannheim, Germany) is then added to each well at a final concentration of 9%, and the cells are incubated for 2 hours at 37°C. This stage allows the mitochondrial dehydrogenase of the living cells to convert WST1 orange tetrazolium salt into crimson formazan. The resulting stained solutions are quantified by dual-beam detection (450 and 690 nm) using a multi-cuvette scanning spectrophotometer.

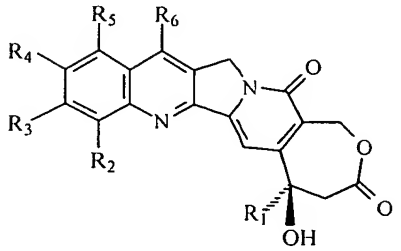
Results

The results shown in the following table are expressed in terms of inhibitory concentration at 50% (IC_{50}, in nM), accompanied by a confidence interval. The inhibitory activities of the adenocarcinoma HT29 cell proliferation of the human colon obtained with the examples of the invention are assessed, these activities being, in an unexpected fashion, superior to the activity of the reference compound described in the PCT Patent Application WO 97/000876.

Example	**substituents (general formula (I))**						**biological activity**	
	R_1	R_2	R_3	R_4	R_5	R_6	**IC_{50} (nM)**	confidence interval
Reference	*Et*	H	H	H	H	H	*30*	*24 – 39*
2	Et	H	F	H	H	H	**2.5**	1.0 – 7.2
5	Et	H	H	H	H	Bu	**16**	11 – 23
6	Et	H	H	H	H	Et	**12**	9 – 14
7	Et	H	H	H	H	Ph	**13**	8 – 19
9	Et	H	H	H	H	4-Me-Ph	**11**	8 – 15
11	Et	H	F	F	H	Ph	**12**	7 – 21
13	Et	H	F	F	H	Bu	**8.5**	4 – 16
15	Et	H	F	F	H	Pr	**11**	7 – 17
16	Et	H	F	F	H	Et	**2.1**	1.5 – 2.7
17	Et	H	F	F	H	$(CH_2)_2TMS$	**5.0**	1.7 – 16
18	Et	H	F	H	F	H	**2.2**	1.4 – 3.3
20	Et	H	F	H	F	Et	**8**	4.7 – 15
22	Et	H	H	H	H	$(CH_2)_2TMS$	**8.6**	3 – 26
23	Et	H	F	H	H	Bu	**9.5**	5 – 17
24	Et	H	F	H	H	Et	**3.5**	2.3 – 5.4

CLAIMS

1. Product characterized in that it is of general formula **(II)** represented below:



(II)

in which

R_1	represents a lower alkyl radical;
R_2, R_3, R_4 and R_5	represent, independently, H or a halogen atom;
R_6	represents H, a linear or branched alkyl radical containing 1 to 12 carbon atoms, a cycloalkyl, lower cycloalkyl alkyl, lower hydroxy alkyl, nitro or $(CH_2)_mSiR_7R_8R_9$ radical, or also an aryl or lower aryl alkyl radical, substituted or non substituted on the aryl group, in which the substituent is a lower alkyl, a hydroxy group or a halogen atom;
R_7, R_8 and R_9	represent, independently, H or a linear or branched alkyl radical containing 1 to 6 carbon atoms;
m	is an integer comprised between 0 and 6;

it being understood that when R_2 represents H, R_6 represents a $(CH_2)_mSiR_7R_8R_9$ radical or a linear or branched alkyl radical containing 7 to 12 carbon atoms;

or salt of said product.

2. Product according to claim 1, characterized in that R_6 represents a $(CH_2)_mSiR_7R_8R_9$ radical.

3. Product according to claim 1 or 2, characterized in that R_1 represents an ethyl radical.

4. Product characterized in that it is one of the following products:

- (5*R*)-5-ethyl-11-fluoro-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-5-ethyl-9-fluoro-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-5-ethyl-8-fluoro-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-12-benzyl-5-ethyl-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-12-butyl-5-ethyl-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-5,12-diethyl-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-5-ethyl-5-hydroxy-12-phenyl-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-12-cyclohexyl-5-ethyl-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-5-ethyl-5-hydroxy-12-(4-methylphenyl)-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-10-chloro-5-ethyl-12-(2-fluorophenyl)-5-hydroxy-12-(4-methylphenyl)-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-5-ethyl-9,10-difluoro-5-hydroxy-12-phenyl-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-5-ethyl-9-fluoro-5-hydroxy-12-phenyl-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-12-butyl-5-ethyl-9,10-difluoro-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-12-benzyl-5-ethyl-9,10-difluoro-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-5-ethyl-9,10-difluoro-5-hydroxy-12-propyl-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-5,12-diethyl-9,10-difluoro-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-5-ethyl-9,10-difluoro-5-hydroxy-12-(2-trimethylsilylethyl)-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-5-ethyl-9,11-difluoro-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-12-butyl-5-ethyl-9,11-difluoro-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-5,12-diethyl-9,11-difluoro-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-5-ethyl-5-hydroxy-12-propyl-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-5-ethyl-5-hydroxy-12-(2-trimethylsilylethyl)-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-12-butyl-5-ethyl-9-fluoro-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-5,12-diethyl-9-fluoro-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

-(5*R*)-5-ethyl-5-hydroxy-12-isopentyl-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino [3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-5-ethyl-12-(4-fluorophenyl)-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino [3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-12-(2,6-difluorophenyl)-5-ethyl-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino [3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-12-(3,5-difluorophenyl)-5-ethyl-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-5-ethyl-5-hydroxy-12-(3,4,5-trifluorophenyl)-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-5-ethyl-5-hydroxy-12-(2,4,6-trifluorophenyl)-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-5-ethyl-5-hydroxy-12-(2,3,5,6-tetrafluorophenyl)-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-5-ethyl-5-hydroxy-12-(2,3,4,5,6-pentafluorophenyl)-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-5-ethyl-9-fluoro-12-(4-fluorophenyl)-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-12-(2,6-difluorophenyl)-5-ethyl-9-fluoro-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-12-(3,5-difluorophenyl)-5-ethyl-9-fluoro-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-5-ethyl-9-fluoro-5-hydroxy-12-(3,4,5-trifluorophenyl)-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-5-ethyl-9-fluoro-5-hydroxy-12-(2,4,6-trifluorophenyl)-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-5-ethyl-9-fluoro-5-hydroxy-12-(2,3,5,6-tetrafluorophenyl)-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-5-ethyl-9-fluoro-5-hydroxy-12-(2,3,4,5,6-pentafluorophenyl)-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-5-ethyl-9,10-difluoro-12-(4-fluorophenyl)-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-12-(2,6-difluorophenyl)-5-ethyl-9,10-difluoro-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-12-(3,5-difluorophenyl)-5-ethyl-9,10-difluoro-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-5-ethyl-9,10-difluoro-5-hydroxy-12-(3,4,5-trifluorophenyl)-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-5-ethyl-9,10-difluoro-5-hydroxy-12-(2,4,6-trifluorophenyl)-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-5-ethyl-9,10-difluoro-5-hydroxy-12-(2,3,5,6-tetrafluorophenyl)-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-5-ethyl-9,10-difluoro-5-hydroxy-12-(2,3,4,5,6-pentafluorophenyl)-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-5-ethyl-9,11-difluoro-12-(4-fluorophenyl)-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-12-(2,6-difluorophenyl)-5-ethyl-9,11-difluoro-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-12-(3,5-difluorophenyl)-5-ethyl-9,11-difluoro-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-5-ethyl-9,11-difluoro-5-hydroxy-12-(3,4,5-trifluorophenyl)-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-5-ethyl-9,11-difluoro-5-hydroxy-12-(2,4,6-trifluorophenyl)-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-5-ethyl-9,11-difluoro-5-hydroxy-12-(2,3,5,6-tetrafluorophenyl)-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-5-ethyl-9,11-difluoro-5-hydroxy-12-(2,3,4,5,6-pentafluorophenyl)-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-5-ethyl-9-fluoro-5-hydroxy-12-propyl-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-5-ethyl-9-fluoro-5-hydroxy-12-(3,3,3-trifluoropropyl)-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-5-ethyl-9-fluoro-5-hydroxy-12-isopentyl-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino [3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-5-ethyl-9-fluoro-5-hydroxy-12-pentyl-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino [3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-5-ethyl-9-fluoro-5-hydroxy-12-phenethyl-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino [3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-12-decyl-5-ethyl-9-fluoro-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-12-(2-cyclohexylethyl)-5-ethyl-9-fluoro-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-12-(3,3-dimethylbutyl)-5-ethyl-9-fluoro-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-5-ethyl-9,10-difluoro-5-hydroxy-12-propyl-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-5-ethyl-9,10-difluoro-5-hydroxy-12-(3,3,3-trifluoropropyl)-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-5-ethyl-9,10-difluoro-5-hydroxy-12-isopentyl-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-5-ethyl-9,10-difluoro-5-hydroxy-12-pentyl-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-5-ethyl-9,10-difluoro-5-hydroxy-12-phenethyl-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-12-decyl-5-ethyl-9,10-difluoro-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-12-(2-cyclohexylethyl)-5-ethyl-9,10-difluoro-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-12-(3,3-dimethylbutyl)-5-ethyl-9,10-difluoro-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-5-ethyl-9,11-difluoro-5-hydroxy-12-propyl-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-5-ethyl-9,11-difluoro-5-hydroxy-12-(3,3,3-trifluoropropyl)-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-5-ethyl-9,11-difluoro-5-hydroxy-12-isopentyl-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-5-ethyl-9,11-difluoro-5-hydroxy-12-pentyl-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-5-ethyl-9,11-difluoro-5-hydroxy-12-phenethyl-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-12-decyl-5-ethyl-9,11-difluoro-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-12-(2-cyclohexylethyl)-5-ethyl-9,11-difluoro-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-12-(3,3-dimethylbutyl)-5-ethyl-9,11-difluoro-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

or of a salt of said product.

5. Product according to claim 4, characterized in that it is one of the following products:

- (5*R*)-12-butyl-5-ethyl-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-5,12-diethyl-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-5-ethyl-5-hydroxy-12-phenyl-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-5-ethyl-9,10-difluoro-5-hydroxy-12-phenyl-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-12-butyl-5-ethyl-9,10-difluoro-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-5-ethyl-9,10-difluoro-5-hydroxy-12-propyl-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-5,12-diethyl-9,10-difluoro-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-5-ethyl-9,10-difluoro-5-hydroxy-12-(2-trimethylsilylethyl)-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-5,12-diethyl-9,11-difluoro-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-5-ethyl-5-hydroxy-12-(2-trimethylsilylethyl)-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-12-butyl-5-ethyl-9-fluoro-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-5,12-diethyl-9-fluoro-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

or of a salt of said product.

6. Product according to claim 5, characterized in that it is one of the following products:

- (5*R*)-12-butyl-5-ethyl-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-5-ethyl-9,10-difluoro-5-hydroxy-12-phenyl-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-12-butyl-5-ethyl-9,10-difluoro-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-5-ethyl-9,10-difluoro-5-hydroxy-12-propyl-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-5,12-diethyl-9,10-difluoro-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-5-ethyl-9,10-difluoro-5-hydroxy-12-(2-trimethylsilylethyl)-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

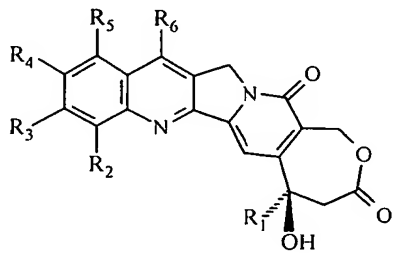
- (5*R*)-5,12-diethyl-9,11-difluoro-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-12-butyl-5-ethyl-9-fluoro-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

- (5*R*)-5,12-diethyl-9-fluoro-5-hydroxy-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino[1,2-*b*]quinoline-3,15-dione;

or of a salt of said product.

7. Process for the preparation of a product of general formula **(I)**,

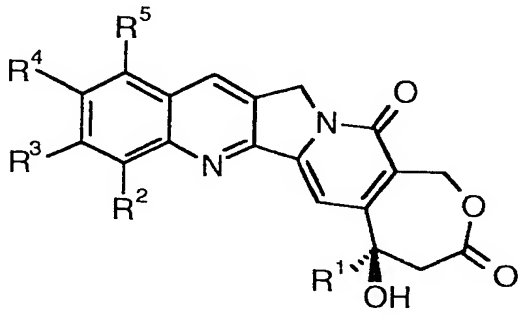


(I)

in which

R_1	represents a lower alkyl radical;
R_2, R_3, R_4 and R_5	represent, independently, H or a halogen atom;
R_6	represents H, a linear or branched alkyl radical containing 1 to 12 carbon atoms, a cycloalkyl, lower cycloalkyl alkyl, lower hydroxy alkyl, nitro or $(CH_2)_mSiR_7R_8R_9$ radical, or also an aryl, or lower aryl alkyl, substituted or non substituted on the aryl group, in which the substituent is a lower alkyl, a hydroxy group or a halogen atom;
R_7, R_8 and R_9	represent, independently, H or a linear or branched alkyl radical containing 1 to 6 carbon atoms;
m	is an integer comprised between 0 and 6;

characterized in that a compound of formula



(IV)

in which R_1, R_2, R_3, R_4 and R_5 have the meaning indicated above, is treated in a strongly acid medium in the presence of an iron (III) salt and a precursor of the free radical $R_6^{\bullet}$, preferably R_6-CHO, by a solution containing hydroxide or alkoxide radicals.

8. As a medicament, product according to any one of claims 1 to 6, or a pharmaceutically acceptable salt of said product .

9. Pharmaceutical composition containing, as active ingredient, at least one compound according to one of claims 1 to 6.

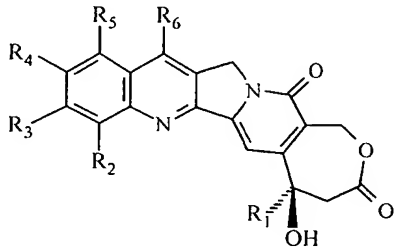
10. Use of a compound according to one of claims 1 to 6 for the preparation of antitumoral medicaments.

11. Use of a compound according to one of claims 1 to 6 for the preparation of antiviral medicaments.

12. Use of a compound according to one of claims 1 to 6 for the preparation of antiparasitic medicaments.

hydroxylactonic analogues of camptothecin, the biological activity of which, expressed for example in terms of inhibitory concentrations on the proliferation of tumoral cell colonies, is, unexpectedly, superior to the activity of compounds which are already known. Finally, a subject of the invention is the compounds previously mentioned as medicaments, their use for the production of medicaments as well as pharmaceutical compositions containing them.

The invention firstly relates to the compounds of general formula **(I)**



(I)

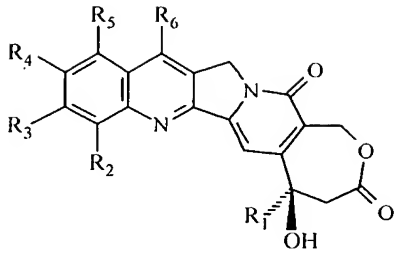
in which

R_1	represents a lower alkyl radical;
R_2, R_3, R_4 and R_5	represent, independently, H or a halogen atom;
R_6	represents H, a linear or branched alkyl radical containing 1 to 12 carbon atoms, a cycloalkyl, lower cycloalkyl alkyl, lower hydroxy alkyl, nitro or $(CH_2)_mSiR_7R_8R_9$ radical, or also an aryl, or lower aryl alkyl radical, substituted or non substituted on the aryl group in which the substituent is a lower alkyl, a hydroxy group or a halogen atom;
R_7, R_8 and R_9	represent, independently, H or a linear or branched alkyl radical containing 1 to 6 carbon atoms;
m	is an integer comprised between 0 and 6;

it being understood that when R_3 and R_4 represent two fluorine atoms or two hydrogen atoms, R_6 does not represent H;

or the salts of the latter.

By lower alkyl radical is meant in the present Application a linear or branched alkyl radical containing 1 to 6 carbon atoms. The term cycloalkyl designates a ring with 3 to 7 carbons, such as for example the cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl groups. The term aryl designates a mono-, di- or tricyclic hydrocarbon compound with

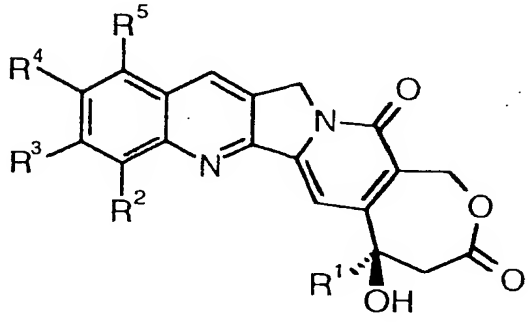


(I)

in which

R_1	represents a lower alkyl radical;
R_2, R_3, R_4 and R_5	represent, independently, H or a halogen atom;
R_6	represents H, a linear or branched alkyl radical containing 1 to 12 carbon atoms, a cycloalkyl, lower cycloalkyl alkyl, lower hydroxy alkyl, nitro or $(CH_2)_mSiR_7R_8R_9$ radical, or also an aryl or lower aryl alkyl radical, substituted or non substituted on the aryl group, in which the substituent is a lower alkyl, a hydroxy group or a halogen atom;
R_7, R_8 and R_9	represent, independently, H or a linear or branched alkyl radical containing 1 to 6 carbon atoms;
m	is an integer comprised between 0 and 6;

can also be obtained by a new process, characterized in that a compound of formula



(IV)

in which R_1, R_2, R_3, R_4 and R_5 have the meaning indicated above, is treated in a strongly acid medium in the presence of an iron (III) salt and a precursor of the free radical $R_6^{\bullet}$, by a solution containing hydroxide or alkoxide radicals.